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Annotations

Blood pressure *Dillon* 347

Brittle or battered *Carty* 350

Inequalities in child health *Wadsworth* 353

Original articles

Preschool vision screening. service in need of rationalisation
ewart-Brown, Haslum, and Howlett 356

ptopril in heart failure secondary a left to right shunt
aw, Wilson, and Dickinson 360

tificial ventilation in severe pertussis
llis, Grattan-Smith, and Kilham 364

Pulmonary function in children after neonatal meconium aspiration syndrome
acfarlane and Heaf 368

Teenage sexual intercourse and pregnancy
urtis, Lawrence, and Tripp 373

Parental diary of infant cry and fuss behaviour
rr, Kramer, Boisjoly, et al 380

ant feeding and allergy
skelly, Burr, Vaughan-Williams, et al 388

onatal patient triggered ventilation
eenough and Pool 394

inary creatinine excretion in the newborn
Dahhan, Stimmler, Chantler, et al 398

ferrals to a regional neonatal ensive care unit
oper, Chiswick, and Sims 403

nical features of conversion disorder
attan-Smith, Fairley, and Procopis 408

Psychological effects of day case surgery compared with inpatient surgery
mpbell, Scaife, and Johnstone 415

Fructosamine or glycated haemoglobin as a measure of diabetic control?
Allgrove and Cockrill 418

Isolated pulmonary histiocytosis
McDowell, Macfarlane, and Martin 423

The trisomy (5)(q31−qter) syndrome: study of a family with a t(5·14) translocation
Elias-Jones, Habibi, Larcher, et al 427

Short reports

Liver failure and Epstein-Barr virus infection
Shaw and Evans 432

Cranial diabetes insipidus in early infancy
Jenkins, Hughes, and Gray 434

Atopic eczema and preterm birth
David and Ewing 435

Mycotic intracranial abscesses during induction treatment for acute lymphoblastic leukaemia
Foreman, Mott, Parkyn, et al 436

Hypothermia and sudden infant death syndrome
Dunne and Matthews 438

Intravenous immunoglobulin for prophylaxis of neonatal sepsis in premature infants
Stabile, Miceli Sopo, Romanelli, et al 441

Varicella gangrenosa
Kidney, Watson, and Nisar 444

Controversy follow up

Sexual abuse—the final word? *Roberts* 446

Current topic

Copper deficiency and non-accidental injury
Shaw 448

Special report

Facts for teachers of children with cancer
Stevens, Kaye, Kenwood, et al 456

Correspondence 459

Book reviews 463

British Paediatric Association: 60 years 464

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Annotations

Blood pressure

The National Heart, Lung and Blood Institute, Bethesda, has commissioned two reports of the Task Force on Blood Pressure Control in Children in the last decade. The first report appeared in 1977 and enjoyed wide distribution becoming a major reference for blood pressure standards in children.[1] The second report was published last year with, in its own words, the following objectives: (a) to identify the proper techniques for measuring blood pressure in infants, children, and adolescents; (b) to characterise the existing data base on blood pressure distributions throughout childhood and to prepare distribution curves of blood pressure by age accompanied by height and weight information; (c) to recommend blood pressure ranges for children denoting normal, high normal, or hypertensive; (d) to present guidelines for detecting children with hypertension and, at the same time, guard against inappropriate labelling of children as hypertensive who are not hypertensive; (e) to identify the appropriate diagnostic steps to be taken in the evaluation of children with hypertension; and (f) to delineate non-pharmacologic and pharmacologic treatment strategies in the management of children with hypertension.[2] Has it succeeded? Are its standards and recommendations applicable to European and, in particular, British children? The answers to these questions are not straightforward but might be summed up as 'not quite' and 'possibly'.

The data used for the 1987 report were taken from nine different studies performed in the United States and Great Britain involving more than 70 000 white, black, and what are described as Mexican-American children.[3–13] The British source was the Brompton study[11–13] involving 7804 subjects from birth to 3 years of age when material was extracted from it for the task force report. Most of the data are, hence, from North American studies, which may or may not be relevant to other parts of the world. Furthermore, the report appears to be written with the United States paediatrician in mind who, unlike his counterparts in many other countries, will be regularly reviewing 'well' children as opposed to only seeing referred 'sick' children as, for example, in the United Kingdom. This places a different emphasis on recommendations especially in the context of 'screening'.

Measurement technique

The most practical technique for measurement of blood pressure is the mercury sphygmomanometer, although for young children accurate recordings may only be possible using the Doppler ultrasound. An appropriate compression cuff is essential, and a useful rule of thumb is to use the largest cuff width that covers the upper arm yet still allows the bell of the stethoscope to be placed over the brachial artery in the antecubital fossa. There is not much argument with the task force in this respect, although it does dwell on the diastolic measurement, which is usually less accurately recordable and less important than the systolic value.[14]

Blood pressure

Amazingly the task force, although extolling the virtues of several blood pressure recordings in an individual child before drawing conclusions about the height of the blood pressure, have used the first blood pressure reading in the 70 000 subjects to prepare its standards because in one of the nine studies used only one blood pressure measurement per subject was available! After this incredible admission it goes on to generate percentiles of the age and sex specific blood pressure distributions by complex multiple regression and spline fitting methods shown by a series of rather small figures with charts for boys and girls from birth to 12 months, 1–13 years, and 13–18 years. These charts only give the 50th–95th percentiles with no thought given to the importance of identifying 'hypotension' and irritatingly a change from the Korotkoff phase IV (muffling) to phase V (disappearance) for diastolic blood pressure at the age of 13 years. Having identified normality as systolic or diastolic blood pressure of less than the 90th percentile and high normal blood pressure between 90th and 95th percentile, hypertension is defined as systolic or diastolic blood pressure, or both, equal to or greater than the 95th percentile for age and sex on at least three occasions. In an attempt to incorporate the important contribution of body size into the analyses the task force have added the 90th percentile details of height and weight for normal children at the bottom of the charts to help with the interpretation of blood pressure values of an individual child. It would have been so much more helpful if it had considered generating percentile charts relating blood pressure to height (or some other index of body size) rather than age: this has been incorporated in the charts produced by Andre *et al*[15] in France and eliminates the errors of age related percentiles and the resulting cumbersome technique to factorise for size of the task force.

Guidelines for detecting children with hypertension

The task force does not recommend mass community blood pressure screening programmes for children and adolescents. It does, however, focus on surveillance of blood pressure of children under continuous care by a primary physician in the United States and recommends, in accordance with the guidelines of the American Academy of Pediatrics, annual determinations of blood pressure in children from 3–20 years of age by their primary physicians. What is this if it is not screening? Clearly these recommendations are of no relevance to countries in the world where primary physicians are predominantly concerned with treating the sick rather than undertaking health checks on well children.

What is appropriate for the United Kingdom? Two working parties (BPA Working Party on Child Health Surveillance and the British Hypertension Society Working Party on Blood Pressure Measurement) are currently considering this matter but have not made their recommendations. Meanwhile it would seem reasonable for all sick children to have their blood pressure measured whenever there is an indication for a general medical examination. As far as screening for hypertension is concerned this has to be considered in relation to the likely prevalence of the disorder. It has been suggested that the prevalence of hypertension in school children is of the order of 1%[16] but in only 10% of these children will the blood pressure be appreciably increased and require treatment. Most children with mild increases in blood pressure will turn out to have primary (essential) hypertension. The important 0·1% of children with more severe hypertension, usually secondary in origin, will have renal disease as the commonest cause. There are certainly advantages in detecting these severely hypertensive children but the cost-benefit ratio in identifying those with primary hypertension remains unclear.[17] In the present state of knowledge it cannot be recommended that all children should have their blood pressures measured at school medical examinations. As it is not difficult to measure blood pressure, however, the Working Party of the British Hypertension Society concerned with blood pressure measurement in children are likely to suggest that individual authorities decide on a policy of screening in childhood, balancing cost against demands on limited resources and bearing in mind the facilities locally for investigation of children in whom apparent hypertension is identified. There are, however, certain children who ought to have regular blood pressure measurements undertaken including those in whom a high blood pressure has been previously detected; those with renal or cardiovascular disease; those with diabetes or neurofibromatosis, and those with a family history of hypertension.

Investigation and treatment

Justification for investigation according to the task force unusually emphasises the importance of a diastolic blood pressure of greater than the 95th percentile whereas on this side of the Atlantic most workers in the field would use the systolic value. The investigations recommended, should hypertension be detected, differ in a number of respects to those agreed on at the Second International Symposium on Hypertension in Children and Adolescents in Heidelberg in 1985[18] with surprisingly no form of renal imaging, plasma renin or catecholamine measurements included in the initial screening procedures. These would certainly be part of the basic investigative protocol in the United Kingdom with more complex tests added subsequently if indicated.[19]

The emphasis on non-pharmacological treatment where indicated is laudable but only appropriate, in isolation, for mild hypertension. This type of treatment surprisingly, seems to be recommended by the task force for any children with systolic or diastolic blood pressure, or both, greater than the 90th percentile. For more severe increases in blood pressure, a 'stepped care' approach for drug treatment is suggested, although the drug choices and dosages are different and, at times, modest compared with European experience.[19] Intravenous labetalol and sublingual nifedipine for severe hypertension are conspicuous by their absence and there is inadequate guidance about inappropriate drugs in children and about side effects.

Task force and the United Kingdom

Although welcome, the Report of the Second Task Force on Blood Pressure Control in Children must be viewed circumspectly by paediatricians and those involved in the community child health services in the United Kingdom. In particular, the age specific percentile charts may not reflect blood pressure norms for British children, quite apart from criticism of them in terms of relating blood pressure to age as opposed to height. There may be an argument, in view of the former, for utilising British age related systolic blood pressure charts for younger children,[20] or, in view of the latter, for adopting the French charts, which are commonly used in Europe.[15] The recommendations concerning screening are acceptable even though the reasoning behind such decisions in the United Kingdom may be rather different from that in the United States. Investigation and treatment proposals should be viewed in the context of current practice in Britain, which differs in a number of respects to the North American recommendations.

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Brittle or battered

There has recently been considerable comment in the national and medical press about the differential diagnosis of the fractures of non-accidental injury in infants,[1–3] and it has been stated that many of these infants are suffering from copper deficiency or a mild form of osteogenesis imperfecta. Clinical experience and a careful review of the literature, however, would indicate that these conditions should not be confused with non-accidental injury.

The diagnosis of non-accidental injury is not made lightly, but certain clinical findings must raise the question of the diagnosis. These include torn frenulum of the lip, unexplained bruising, retinal haemorrhages, and delay in seeking medical attention for fractures. In these circumstances radiography of the skeleton is part of the routine clinical assessment. The finding of metaphyseal fractures or fractures in different stages of repair in the presence of normal bones without a history of injury is regarded as being diagnostic of non-accidental injury. Other fractures that should strongly suggest non-accidental injury are comminuted wide skull fractures, scapular fractures, and fractures of the outer end of the clavicle. Similarly it is strongly suggested by rib fractures.[4–8] Rib fractures only occur in children with normal bones in response to severe trauma such as road traffic accidents. Even the compression forces used in vigorous cardiopulmonary resuscitation rarely produce them. In one series of 113 children no rib fractures were found in children who had undergone cardiopulmonary resuscitation.[9] I have never personally seen a fractured rib after this procedure.

A full review of the radiological manifestations of child abuse can be found in a recently published book by Kleinman.[10] It has been said that the only reason a differential diagnosis is considered is the reluctance to accept the implications of the bony lesions.[11]

Copper deficiency

A full review of copper deficiency is published elsewhere in this issue (p 448). This annotation gives a synopsis of the salient clinical and radiological features. The reported clinical features of copper deficiency in infants are psychomotor retardation, hypotonia, pallor, hypopigmentation of skin and hair, prominent scalp veins, sideroblastic anaemia resistant to iron treatment, and neutropenia (J C L Shaw, personal communication).[12–19] The radiological changes are those of osteoporosis, fraying and cupping of the metaphyses, spur formation, periosteal reaction, and fractures.[12–26]

About 40% of reported cases of copper deficiency are in premature infants of whom about 25% are on long term parenteral nutrition (J C L Shaw, personal communication).[12–19] There have been cases in full term infants who have had a severe dietary deficiency of copper.[18 19 27 28] The median age at presentation is a mean of 8·3 months for full term infants and 3·0 months for preterm infants. Copper deficiency has never been described in an infant fed exclusively breast milk or in a full term infant fed a formula known to contain adequate amounts of copper. Since 1983 most, though not all, formula milks freely available in the United Kingdom contain enough copper to prevent dietary deficiency.

Plasma copper concentrations are low at birth but reach adult concentrations by 4 months[29]; they can be reliably measured by atomic absorption spectrophotometry. When this method is used no child has been reported with the syndrome of copper deficiency with a plasma concentration of greater than 43 μg/dl for term infants and 33 μg/dl for preterm infants (J C L Shaw, personal communication). In all cases the response to treatment either by the introduction of copper supplements or dietary improvement has been prompt with a reticulocytosis, a rise in haemoglobin and neutrophil count, and resolution of the bone changes. There are no reported cases of fractures occurring as a late sequel to proven copper deficiency.

The bone disease of copper deficiency is a metabolic disease. The osteoporosis affects all bones and the metaphyseal fraying affects the growing ends.[12–25] These features are most easily seen in the distal radius and ulna, though the fraying is more pronounced in the ulna.[22] The fraying leads to sickle shaped spur formation and fractures may occur through these. These fractures do not resemble the corner fractures of non-accidental injury. In non-accidental injury the child's bone texture is normal, and there is no cupping or fraying of the metaphysis where there is a fracture. The appearances of copper deficiency have been described as scorbutic, as in both there is severe osteopenia and spur formation with corner fractures. There is a superficial resemblance but the radiological appearances are quite distinct. In scurvy there is no fraying of the metaphyses and the epiphyses have a distinctive etched appearance with a sharp outline and 'washed out' centre. Scurvy can also be easily excluded by biochemical tests.

Skull fractures have not been described in infants with copper deficiency, but they are a common finding in non-accidental injury. The presence of normal bone and in particular the presence of normal wrists and knees renders the diagnosis of copper deficiency of sufficient severity to cause fractures unlikely and this can be stated even in the absence of a serum copper concentration The absence of anaemia and neutropenia and the physical stigmata further make the diagnosis virtually untenable.

Osteogenesis imperfecta

The diagnosis of severe forms of osteogenesis imperfecta is indisputable by a radiologist or clinician. Milder forms of the disease can be difficult to diagnose and often a diagnosis can only be made with time. Most children with mild osteogenesis imperfecta do not present with fractures early in life but tend to fracture between toddling and adolescence.

There is, as yet, no freely available biochemical test for the disease although interesting research is continuing in the fields of collagen chemistry and genetic markers. Until this work produces a test that is freely and quickly available in a general hospital, the diagnosis of osteogenesis imperfecta will have to be made on clinical and radiological grounds.

Considerable genetic heterogeneity is present in osteogenesis imperfecta. Four genetic subgroups have been identified.[30] Within the groups there is a considerable range of severity, and it is this that leads to the potential diagnostic confusion it is important for both paediatrician and radiologist to actively consider the question of osteogenesis imperfecta in any child suspected of non-accidental injury. The clinical diagnosis of osteogenesis imperfecta rests on the findings of blue sclera in certain cases, a large fontanelle, excessive joint laxity, small stature, and dentinogenesis imperfecta. Some patients with the disease have normal sclera. The clinical manifestations are very variable.

Dentinogenesis imperfecta of osteogenesis imperfecta is best confirmed by a dentist with a particular interest in the subject. Not all pitted teeth are due to it and an expert opinion should be sought in all cases with teeth defects where the diagnosis is in dispute. Many of these cases occur before tooth eruption and dental changes and x radiography is, therefore, of no diagnostic help.

Fractures both accidental and non-accidental can occur with or without bruising over a fracture site. The presence or absence of bruising over a fracture site gives no indication as to the cause of a fracture. The fact that patients with osteogenesis imperfecta may have a tendency to bruise easily is irrelevant in the context of fractures.

A family history of fractures and deafness is often quoted as supportive evidence of the diagnosis of osteogenesis imperfecta and in many cases this is helpful. However, a detailed history of the type of deafness or the way in which the fractures were sustained should be taken. The fact that a relative sustained fractures when falling from a tree or in a motor bike accident does not mean that there is a family history of the disease.

Children with osteogenesis imperfecta may sustain fractures with minimal force but in those with the mild form of the disease these tend to occur when the child is toddling or walking and not confined to a cot. The fractures of osteogenesis imperfecta are mostly in the diaphyses of the long bones. Metaphyseal fractures are rare and when they do occur there is evidence of gross change of the disease.[31] Osteoporosis in mild cases of osteogenesis imperfecta may be mild but some alteration of the trabecular pattern is usually identifiable. Wormian bones are an almost constant finding in osteogenesis imperfecta,[31 32] and they have a different distribution to those seen as developmental variants.[32] Children who have sustained non-accidental injury are unlikely to sustain further fractures while in care Where a diagnosis of non-accidental injury is made incorrectly in a child with osteogenesis imperfecta fractures are likely to continue to occur after the child has been placed in care.

It can be seen, therefore, that there are distinguishing features between the three conditions and diagnostic confusion should not arise.

It is vital that non-accidental injury is not over diagnosed. Most paediatricians and radiologists will not make the diagnosis unless they have strong grounds for it and will err on the side of caution if in doubt.

When a case is contested, before court proceedings start, it is essential that the barrister and solicitor are properly briefed, so that they fully understand the medical evidence. Medical evidence is given not to seek retribution for the child's injury but to arrange for proper protection for that child, hopefully with rehabilitation of the family unit. It is difficult for non-medically trained judges and juries to understand the subtleties of radiological changes and the nuances of clinical practice.

Yet it is on this evidence that the outcome of a case often rests and will continue to do so while the adversarial system of the law continues for such cases.

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Archives of Disease in Childhood, 1988, **63,** 353–355

Inequalities in child health

It is odd that discussions on what are usually called 'inequalities in child health' have been concerned mainly with mortality and morbidity and relatively little with health. This is particularly curious when the great improvements in child health achieved since the NHS began have considerably reduced the proportion of children who are nowadays seriously ill. Generally in such discussions health itself is taken to be shown by height, or by the rate of height growth, or by the absence of illness, but these are now scarcely sufficiently discriminating indicators for population studies. Recent thinking about the development of adult chronic illness shows why the measurement of child health should be developed to a point where we could differentiate degrees of health in childhood and see whether they were distributed evenly across all social groups, and we could therefore ask whether the proportion of the most healthy is increasing or not.

It is well documented that height, one of the traditional measures of child health, varies considerably with social class in childhood,[1] and that the tempo of height growth is similarly varied, being slowest in the lowest social classes and greatest in the highest classes.[2] It is also well documented that height is related to health in later life, in the sense that shortness of stature is associated with higher mortality at any given adult age.[3] But although depletion or enhancement of quality of skeletal structure and of stature may occur during adult life through eating, exercise, and smoking habits, the limits of growth in height may be achieved only during a relatively short period of time in childhood. Therefore social inequality in achievement of height growth is indicative of risk of social inequality in health in adult life.

This example brings together the important notions of a critical period, during which partially inherited potential is developed through environmental influences, particularly those involving individual choice, in this case choice of food and exercise. During childhood, when these choices are largely a matter for the child's mother, she may well be influencing both the extent of fulfilment of developmental potential and the child's taste in such habits now and possibly even in later life. The relative contribution of these elements to the observed social class differences in growth rates and in height is so far not known

It begins now to look as if there are other aspects of childhood health that, like height, may well have long term implications for health. Although few other areas of development are quite so circumscribed in time as physical growth, the model of a potential in which the degree of fulfilment is affected by environmental factors has been often used in other aspects of child development, although the inclusion of habit behaviour as part of the environment has been relatively rare, even though it is likely to be of considerable importance.

In the study of obesity, where research into habit behaviour is of relevance, it seems now that early adult onset is far more common than childhood obesity,[4] and may even prove to be a greater risk for chronic illness than childhood onset obesity. Although the dynamics of the aetiology of obesity are still by no means clear, there is no doubt that the secular trend in prevalence is rising in childhood and in adult life, and that it is rising fastest in the lower social groups.[4–6] Childhood and adult obesity each carry appreciable risks to health.[6]

Blood pressure also looks as if it may prove to follow a pattern of childhood establishment to a certain extent.[7] It too has an intrafamilial element and the blood pressure measurements of each individual tend to 'track' from some, as yet undefined, point in childhood or adolescence into adult life,[8] and blood pressure is strongly associated with such environmental choice factors as eating and exercise, with which it is also related through its association with obesity. Blood pressure is appreciably higher in the manual social classes, but seems likely to be reduced in those from lower socioeconomic families of origin who achieve a relatively high standard of education.[9]

Adult respiratory capability may also fit with the notion of a critical or particularly sensitive period in childhood, during which time adverse environmental factors may have a long term influence. Childhood chest illness and poor home circumstances have been found to be associated with relatively poor respiratory function in adult life. These early life experiences were found to be independently associated with adult respiratory function, and they were aggravated in their effect by poor home circumstances in adult life and by cigarette smoking. The risk of this chain of problems is much higher in families in the lowest social classes and in the poorest home environments.[10 11]

Recent epidemiological work that uses national mortality data reinforces the idea of the probable importance of health in childhood for health in adult life. Cohorts of children who grew up in times of high infant death rates from bronchitis or pneumonia and survived, have been found in their adult years to have a high risk of mortality from bronchitis or emphysema; as these infant death rates fell from 1900 onwards so corresponding death rates from the same conditions fell in the next generation: from 1940.[12] Analysis of secular trends in mortality data has suggested that the current distribution of ischaemic heart disease reflects poor social conditions in early life, particularly poor nutrition in childhood, among those now at the ages of greatest risk for this condition.[13]

A review of research on long term effects on pregnancy outcome and fetal development concludes that there is a mass of evidence that shows the importance of the mother's childhood health.[14] Low birth weight, which is more prevalent in low social class mothers and those from the poorest home circumstances, has been found to be associated in due course with relatively increased risk of poor or abnormal outcome of pregnancy in these same individuals.[14] There is therefore evidence for intergenerational links in child health.

This increasing and necessary body of research into health during the course of the individual's lifetime shows not only the fundamental nature of health in childhood for later life but also the extent of social inequalities in child health, particularly in those aspects that may affect health in adult life. In some conditions, such as obesity, there may even be an adverse trend over time.

It is therefore appropriate now to argue that we should no longer rely on the negative measures of health as absence of illness nor on height as a sufficient indicator of health by implication. An improved knowledge is required of those dimensions of children's health that are most likely to be associated with their health in the long term for two reasons. First, because from what we know of these dimensions some children still have a better opportunity than others for good health; second, because it looks, from the evidence of one-off studies, as if some of these important aspects of child health are changing, and at present there is no systematic way of monitoring either improvements or adverse change.

The first stage in improving our knowledge would be to establish a monitoring system to obtain appropriate data from small samples that were representative of the population of children aged 5, 10, and 15 years. Information might, for instance, be collected on height, weight, and other appropriate anthropometric measures, on respiratory function, blood pressure, and possibly some form of exercise test. The opportunity should also not be lost to collect data on health associated behaviour that might include a mother's report on her child's diet and exercise habits and on parental smoking, as well as a small amount of data on the home and social circumstances of the family. This would provide information on the state of child health and on its variation across social and family circumstances, which would complement the work of the British Paediatric Association's Surveillance Unit on morbidity in severe conditions that have a very low prevalence, and the Registrar General's collection of mortality information.

A repeat of this same study design on new samples selected in the same way five years later would offer the opportunity to assess the extent of change in these measures and the rate at which change had occurred in different social groups. This would be primarily an epidemiological design of data collection and not a system for collecting information in a case finding way. For some purposes, however, it might also be valuable to recontact children in some of the original samples measured for the first stage, in order to investigate individual rates of change. But that would not be necessary in achieving the first objective of measuring the social distribution of child health and the rates of change of its components and thus amassing some information that may provide data about adult health in future years.

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Original articles

Preschool vision screening: a service in need of rationalisation

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SUMMARY A survey of health districts in England and Wales was carried out at the end of 1984 to ascertain among other things the range of current programmes for preschool vision screening. The response rate was 81·3%. Altogether 94% of districts reported screening for both reduced visual acuity and squint; two districts screened for neither. A great variety of different types of tests were in use and screening was carried out at a variety of different ages. A high proportion of districts were screening children for reduced visual acuity in infancy, although screening tests applicable at this age have not been shown to be effective. Districts screened for squint between one and four times. Collection of routine monitoring information by districts was poor.

The term preschool vision screening is vague. It can be used to cover a great variety of activities from inspection of the visible structures of the eye and the alignment of the two visual axes to sophisticated tests of visual acuity and ocular muscle balance. It also covers systematic attempts to screen entire populations at specific ages with standardised instruments, and the application of one or more clinical tests of visual ability to children who present for developmental surveillance.

The term is most commonly applied to tests designed to identify ocular muscle imbalance (manifest or latent squint) the commonest of which is the cover test, or tests designed to identify reduced visual acuity. The latter can be caused by many different opthalmological conditions, but in the preschool period it is most commonly due to amblyopia or refractive error.

The use of the term 'preschool vision screening' is also complicated by the fact that not all education authorities have the same policies on age at school entry. Children may start school at any age from 4 to 5½ years. Some parts of the country are well supplied with nursery school places and in these a high proportion of children may be in nursery school from the age of 3 years. Some districts regard the latter as preschool children, others as schoolchildren.

Attempts have been made to establish a national pattern for preschool vision screening with respect to the age at which children should have their vision tested. Both *Prevention in the Child Health Services*[1] and the 1980 *Health Visitors' Association Report*,[2] recommended that all children should have their visual acuity tested and the cover test perfomed at 8 and 18 months of age and again at 2½ to 3 years and 4½ to 5 years. The Court Report[3] recommended that 'tests of vision' be administered at 7 to 9 months and at 2 to 3 years. None of these reports have been specific about which tests should be used; indeed in the report of the Health Visitors' Association a comment was made to the effect that 'while preparing this paper the Association was acutely aware of the lack of systematic and scientifically based information concerning . . . the most valid and reliable tools for these procedures.'

The present study was carried out to document the current range of preschool vision screening practices. The method of investigation used, a questionnaire survey, has appreciable limitations in the study of an activity as diffuse as preschool vision screening. In particular it is difficult from a survey of this kind to identify districts with precisely comparable screening programmes. As a method of obtaining a broad picture of current programmes, however, and of identifying specific districts that are worthy of further study a questionnaire survey is the method of choice.

Methods

In November 1984 a detailed questionnaire was sent to the district medical officers of all health districts in England, Wales, and Scotland asking for information about their vision and hearing screening programmes for preschool and schoolchildren. Responses to questions on preschool vision screening from health districts in England and Wales are presented in this paper.

Altogether 165 districts returned a completed questionnaire: an overall response rate of 81·3%. One district refused to participate; and 37 failed to return their questionnaires after two reminders. There was no significant difference between response rates in different parts of the country, 11 out of a total of 15 geographical units (14 regional health authorities and Wales) had response rates of 80% or more. The four regions with low response rates were Mersey (40%), North West and North East Thames (both 69%), and Trent (75%). The response rate to individual questions in the survey varied; non-respondents are therefore separately identified in each table.

Results

Altogether 155 (94%) districts screened for both reduced visual acuity and for squint; a further five (3%) screened for reduced visual acuity alone, and a further three (2%) for squint alone. Two health districts reported that they carried out no preschool vision screening. These districts were clear that they made no attempt to screen their entire population either for squint or for reduced visual acuity. In both these districts, however, children at high risk of visual problems and those whose parents were anxious about their visual ability or suspected a squint had their vision tested in child health clinics and both districts carried out screening among the 'at risk' 3 to 5 year olds in nursery school classes and day nurseries.

Table 1 shows the tests used in 160 districts screening for reduced visual acuity. The Sheridan Gardiner letters test was the most common test and was used by 123 districts. Eighty eight districts used the Stycar graded balls test and 75 the Stycar picture matching tests. A total of 13 different types of test were in use. The range of ages at which these tests were used, where they were specified, was wide.

Table 1 *Visual acuity tests used in preschool vision screening (n=160)*

Type of test	*Districts No (%)*	*Age range in months*
Sheridan Gardiner letters	123 (76 9)	24–60
Stycar graded balls	88 (55·0)	0–48
Stycar picture matching	75 (46 8)	7–60
Hundreds and thousands	69 (43·1)	0–36
Catford drum	24 (15 0)	0–48
Matching E's	7 (4 4)	30–60
Kay pictures	6 (3 8)	Not stated
Stycar letters (five and seven letter tests)	5 (3·2)	Not stated
Beale Collins	5 (3 1)	8–60
Snellen	4 (2·5)	Not stated
Ffooks	2 (1 3)	36
Leeds picture test	1 (0 6)	Not stated
Stycar miniature toy test	1 (0·6)	Not stated

No visual acuity screening in five districts

Districts were almost equally divided into those who aimed to screen children's visual acuity once, those who aimed to screen twice, and those who aimed to screen three or more times (table 2). Among those testing only once the age at testing varied from 8 to 52 months. The most common age for a single test was 36 months (19 districts). Among districts testing children's visual acuity twice the ages at testing were also very varied The age at first test varied from 0–36 months, and at the second test, 10–60 months. Eight and 36 months was the most common combination but this was practised in only seven districts, and almost every combination of ages was represented.

Table 3 shows the tests used by the 158 districts who screened for squint. Altogether 145 districts used the cover test at some time in the preschool period. More than half of the districts used the corneal reflection test, and 69 said that they tested for squint by ocular movements. A number of

Table 2 *Visual acuity screens (n=149)*

No of screens	*Districts No (%)*
0	5 (3·4)
1	44 (29 5)
2	46 (30·8)
3	33 (22·1)
4	13 (8·7)
5	7 (4 7)
6	1 (0 7)

Age not specified in 16 districts

Table 3 *Screening tests for squints (n=158)*

Type of test	*Districts No (%)*
Cover test	145 (91 8)
Corneal reflection	110 (69·6)
Ocular movements	69 (43 7)
20D Base out prism	18 (11 4)
Finger nose	17 (10·8)
TNO*	9 (5·7)
Convergence at near	5 (3 2)
Wirt*	4 (2 5)
Lang*	3 (1·9)
Keystone	3 (1 9)

No squint screen in seven districts
*Tests of stereo acuity

Table 4 *Cover test for squint (n=125)*

No of screens	*District No (%)*
0	13 (10·4)
1	50 (40·0)
2	24 (19·2)
3	37 (29·6)
4	1 (0·8)

Not specified in 33 districts, no squint screen in seven districts

districts tested all children using more sophisticated orthoptic tests, the commonest of which was the 20D base out prism.

Some of the districts screening with the cover test used this on a number of occasions (table 4). Among districts in which the cover test was used only once the age at testing varied from 6 to 48 months.

Districts were asked for two simple measurements of their screening programmes. first, the proportion of children in their district screened for squint between 7 to 9 months in the previous year, and second the referral rate from this screening programme. Only 40 (25%) districts screening for squint could provide a figure for the proportion of children screened in the previous year; reported rates varied from more than 95% to 50%. An even smaller proportion (11%) of districts could record a referral rate for this programme; reported rates in the districts which could varied from 1% to 33%

Discussion

Preschool vision screening is routine practice in almost all health districts and a very wide range of programmes exist. Without a 100% response rate the survey cannot provide a precise frequency distribution of districts using different programmes, but it does identify that at least two health districts are doing no vision screening; that at least 21 districts screen for reduced visual acuity on four or more occasions and that at least 38 districts carry out cover testing on three or more occasions

The range of programmes documented in this survey is greater than that documented in the same survey for preschool and school hearing screening and for school vision screening.[4] It cannot be compatible with a cost effective national service; some districts must inevitably be operating programmes that consume many extra resources for very little extra benefit.

The Stycar tests for detecting reduced visual acuity in infancy (0–2 years) were developed as clinical instruments for the assessment of vision in young and handicapped children and not as screening instruments. One study has subsequently attempted to assess the value of these tests in a screening programme.[5] The authors of this study found the tests to be ineffective and recommended that they should not be used for screening. Other experts have now lent support to this recommendation [6] Although discontinuing established practice takes time, one would hope that all the many districts currently using these tests have made plans to discontinue them in the near future.

Available evidence on the efficiency of tests used to screen for reduced visual acuity in the immediate preschool period (3–5 years) is only slightly more encouraging than that for the Stycar tests in infancy.[5 7 8] All available tests give a positive result for an appreciable proportion of children with no abnormality, and miss an appreciable proportion of children with a problem. In well trained hands, however, it would appear that the tests can be used to achieve a reasonable level of efficiency.[9] These programmes can also be criticised on the grounds that treatment for the conditions that are identified (amblyopia and refractive error) may not be very effective. Most trials of treatment for amblyopia including occlusion therapy and stimulation with gratings have been poorly controlled, and even these have shown only a modest improvement in vision [10] Although it is certain that some children treated in some centres do show an important visual improvement it would appear that most children detected in screening programmes benefit only modestly from treatment.[11] The treatment of refractive errors not associated with squint or amblyopia in the preschool period is based entirely on clinical evidence, because no studies have been conducted that show that this condition causes appreciable disability, nor that treatment can reduce it.[12] The combination of imperfect screening tests and relatively poor outcomes of treatment make it difficult to justify visual acuity screening at 3–5 years.

As for amblyopia screening, programmes for the identification of squint can be criticised both on the grounds of low efficacy of screening tests, false positive referrals from the cover test are very common, and on the grounds of low efficacy of treatment. Surgical treatment for this condition is reasonably effective for cosmetically disturbing squint, but this, by definition, does not need a screening programme for its identification. The effectiveness of orthoptic treatment for small angle and latent squints is much less certain, and has not been assessed in the context of the sound knowledge of the natural history of these conditions. For both visual acuity screening at 3–5 years and squint screening at all ages, the definitive studies that might determine exactly how much good they could do to how many children have not been done. Until they are individual districts will have to decide whether they wish to continue running these screening programmes or whether their resources would be better deployed elsewhere.

Reading the scientific literature on preschool vision screening can only leave the reviewer with a feeling that discontinuing all these programmes would do children no harm; this evidence, however, needs to be balanced against the strongly held clinical view that this screening makes an important contribution to child health. In the midst of this dilemma, the two districts who do not screen would appear to offer an excellent opportunity to study 'a natural experiment.' If preschool vision screening programmes do make an important contribution to child health, then the visual health of children in these two districts should be demonstrably worse than that of children elsewhere.

The presentation of results from this survey has in the past invariably stimulated requests to make recommendations about what districts should do. Preschool vision screening has, however, suffered in the past like many of its counterparts in child health from too many recommendations made by too many people on the basis of too little evidence. This survey does not provide additional evidence as to what should and should not be done; it only identifies some significant anomalies in current practice. It is important to accept that we do not know what constitutes the optimum preschool vision programme at present, and that districts will need to make their own judgments as to what should or should not be done. At district level this decision can be based on a knowledge of what other services would need to be sacrificed in order to continue screening. All districts, however, owe it to the public whose time and money is spent on these programmes to provide a system for monitoring their effectiveness and efficiency. Such a system would permit both the staff involved in screening and the general public to review annually the number of children whose health has improved as a result of screening, and the amount of work which has gone into achieving this improvement. These data would help districts considerably in making judgments as to what should and should not be done, but at present they are collected by only a small minority.

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Captopril in heart failure secondary to a left to right shunt

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SUMMARY Captopril was used in 20 infants aged less than 1 year with heart failure secondary to defects with predominantly a left to right shunt that was poorly controlled with digoxin and diuretics. Total daily dose of captopril ranged from 0·88 to 2·5 mg/kg (mean 1·3 mg/kg) in three divided doses. Improvement in the control of heart failure was seen mainly as an increase in the rate of weight gain from a mean of 48 g/week before treatment to 102 g/week on treatment and a decrease in the mean respiratory rate from 68 breaths/minute to 60 breaths/minute. Side effects were seen in four patients—two with asymptomatic mild hypotension, one with renal insufficiency which improved with a reduction in dose, and one with severe oliguria progressing to renal failure. Significant changes in plasma electrolyte concentration did not occur except in the infant who developed acute renal failure.

After encouraging reports on the use of captopril, an angiotensin converting enzyme inhibitor, for the treatment of cardiac failure in adults in both clinical[1] and haemodynamic studies[2] we used this drug in a group of infants with refractory heart failure. All were infants with high pulmonary blood flow and pulmonary hypertension secondary to a congenital cardiac defect with a predominantly left to right shunt.

Patients and methods

Captopril was used in 20 such infants over a three year period from April 1984 to April 1987. Details of diagnosis are given in the table. All were in heart failure, which was not controlled adequately by maximum doses of diuretics and digoxin and all were failing to thrive despite calorie supplementation of their diet. In several cases nasogastric tube feeding was necessary. All were in hospital at the time of introducing captopril so that they could be observed closely for any adverse effects. Before starting captopril urea and electrolytes were checked and recordings made of weight and blood pressure.

The median age at introduction of captopril was 3 months (range 1 to 7 months) with a median weight of 3100 g. The maximum dose of captopril used ranged from 0·88 to 2·5 mg/kg/day with a mean dose of 1·3 mg/kg/day. All the infants were being treated with frusemide (range 2·2 to 8·5 mg/kg/day) and spironolactone (range 1·5 to 10 mg/kg/day) and 12 were receiving digoxin in a maintenance dose of 10 µg/kg/day.

Captopril was introduced in an initial dose of 0·25–0·5 mg/kg/day in three divided doses and blood pressure was checked every 15 minutes for the first few hours. If the blood pressure did not fall by more than 15 mm Hg or below 60 mm Hg systolic the dose was increased by increments of 0·5 mg/kg/day over the course of several days until a satisfactory clinical response had been obtained or to a maximum of 4·0 mg/kg/day. Repeat assessment of full blood count and urea and electrolytes was made at intervals during the dosage increment and subsequently after a few weeks on treatment.

CONTROL OF HEART FAILURE

The degree of control of heart failure was assessed by measurement of heart and respiration rate and the rate of weight gain before and after the introduction of captopril. Mean heart rate and respiratory rate were obtained retrospectively from the nursing charts for a period of three days before captopril and for a similar period after the maximum dose for each patient had been achieved. Weight gain was measured over a four week period before and after the introduction of captopril. The feeding pattern was assessed as being all nasogastric tube feeds, part nasogastric tube feeds or all oral feeding.

Table *Clinical details of infants studied, captopril dose, and weight gain*

Patient No	*Diagnosis*	*Age at start of treatment (months)*	*Maximum captopril dose (mg/kg/day)*	*Weight gain (g/week)*		*Duration of treatment (months)*
				Before	*After*	
1	Ventricular septal defect, patent ductus arteriosus	1	1·5	80	177	3
2	Ventricular septal defect	2	1·2	−50	185	4
3	Ventricular septal defect	2	1·0	55	—	2 days
4	Atrioventricular septal defect	2	1·2	120	43	3
5	Ventricular septal defect	2	1·2	15	128	3
6	Ventricular septal defect	2	0·88	147	44	3
7	Transposition of great arteries, ventricular septal defect	2	1·5	223	238	1
8	Ventricular septal defect	2	1·0	13	60	2
9	Ventricular septal defect	3	2·0	−30	85	8
10	Ventricular septal defect	3	1·5	115	188	2
11	Single ventricle	3	1·0	93	93	3
12	Transposition of great arteries, ventricular septal defect	3	1·2	64	92	1
13	Ventricular septal defect	4	2·5	−105	105	4
14	Ventricular septal defect, double outlet right ventricle	4	1·4	40	105	1
15	Ventricular septal defect	4	1·4	63	−63	4
16	Ventricular septal defect	4	1·0	36	117	3
17	Ventricular septal defect	6	1·1	0	83	3
18	Ventricular septal defect	7	1·3	17	138	3
19	Ventricular septal defect	7	1·1	63	33	2
20	Ventricular septal defect	7	1·2	0	83	3

The infants did not routinely have radiographs taken during the period of observation unless there was a specific indication, and heart size on a chest radiograph could not therefore be used as an indicator of improvement. Similarly as all of these infants had apical mid diastolic murmurs from high pulmonary blood flow it was impossible to use the presence or absence of a third heart sound to assess the degree of heart failure.

Statistical analysis was performed using Student's *t* test.

Results

After exclusion of the one patient in whom treatment was discontinued because of renal failure (see below) the mean rate of weight gain before treatment was 48 g/week compared with 102 g/week in the period after the maximum dose of captopril had been achieved ($p<0{\cdot}02$). Six of the 19 infants showed no change in the rate of weight gain but in the remainder the change was clearly related to the introduction of the drug.

There was no significant difference in the mean (SD) heart rate before (140 (12) beats/minute) and after (135 (10) beats/minute) captopril. The mean respiratory rate on captopril (60 (9) breaths/minute), however, was significantly slower than that recorded before the treatment was initiated (68 (11) breaths/minute) ($p<0{\cdot}05$).

In retrospect it is difficult to make any quantitative assessment of the change in feeding pattern. At the time treatment with captopril was started 10 infants were feeding orally but were unable to manage an adequate intake within a reasonable time of less than 30 minutes Seven of these infants were discharged gaining weight steadily and completing feeds within an acceptable time Two infants admitted on nasogastric tube feeds were discharged on full oral feeding while the remaining seven changed from a pattern where they were virtually entirely tube fed to a pattern where a substantial proportion of their daily milk intake was taken orally

Complications of treatment were seen in four patients. Two infants developed asymptomatic hypotension which responded to discontinuing the drug and restarting on a lower dose. One infant (patient 10) was very sensitive to increments in the dose of captopril developing renal insufficiency (urea 19 mmol/l, creatinine 141 mmol/l) on a dose of 2·2 mg/kg/day which improved when the dose was reduced to 1·5 mg/kg/day Acute renal failure occurred in one infant (patient 3) within 24 hours of starting captopril but fortunately recovered completely on cessation of the drug.

Apart from the two who developed renal impairment or treatment there was no significant change in plasma urea, creatinine or electrolytes following treatment with captopril. No patient became neutropenic on treatment.

Treatment duration has ranged from one to eight months. Fourteen of these infants have undergone surgical treatment for their cardiac problem. Five, with isolated ventricular septal defects, continue on medical treatment and one died after surgery for an unrelated problem. The death of this last patient could not be associated with the use of captopril.

Discussion

Many patients with congenital heart problems require medical treatment for congestive cardiac failure. Digoxin and diuretics have been used for many years but recently the value of this treatment, particularly the use of digoxin, has been questioned.[1] Alternative approaches with vasodilators or inotropic agents have not proved to be entirely satisfactory,[1] but the introduction of angiotensin converting enzyme inhibitors appears to offer some hope of progress.

Captopril blocks the conversion of the inactive peptide angiotensin I to the active peptide angiotensin II with a resulting decrease in peripheral vascular resistance.[3] The production of aldosterone stimulated by angiotensin II is inhibited with a consequent reduction in secondary hyperaldosteronism thereby minimising salt and water retention. As peripheral vasoconstriction[4] and hyperaldosteronism[5] are important features in the pathogenesis of congestive cardiac failure, captopril would appear to be a rational choice of drug for its treatment. It has been used extensively in adults with congestive cardiac failure secondary to coronary artery disease, valvular heart disease, or cardiomyopathy with benefit[2 6] but there have been few reports of its use in children other than in renal parenchymal hypertension where it has been shown to be a safe and effective drug.[7]

These patients in whom we have used captopril have benefited from its use presumably as a consequence of a decrease in left to right shunting after a fall in peripheral vascular resistance. Objective confirmation that this improvement results from a relatively greater decrease in systemic resistance as compared with pulmonary resistance would require an invasive haemodynamic study that we did not consider to be justifiable.

The main objective indications of improvement in the control of cardiac failure have been better weight gain (in 13 infants out of 19) and decreased respiratory rate (in 12 out of 19). It is possible that with time those patients with ventricular septal defects would have improved because of a decrease in the size of the defect. It seems unlikely, however, that this would have occurred within the timescale of a few weeks. Better weight gain might have been a consequence of the hospital admission because of the skill and persistence of experienced nursing staff in feeding 'difficult' babies. Most patients, however, had been in hospital for some time before the introduction of captopril and the change in feeding and weight gain, when it occurred, was always clearly related to the timing of the introduction of the drug.

As captopril inhibits aldosterone production, potassium excretion on captopril treatment is reduced and concomitant treatment with a potassium sparing diuretic is normally contraindicated. It is of interest therefore that although all our patients were on spironolactone at the start of treatment and the dose remained unchanged after captopril was introduced, hyperkalaemia was not a problem except in the two patients who developed transient impairment of renal function. Others have noted improvement in three patients who were receiving digoxin, a loop diuretic, and an angiotensin converting enzyme inhibitor after the introduction of spironolactone.[8] The contraindication to this combination is clearly not absolute and in some circumstances a beneficial effect may be seen.

The results of any retrospective assessment need to be viewed with caution. Nevertheless, our findings are essentially the same as those reported recently by Scammell *et al* in a similar study.[9] We have been encouraged by the response of some patients to captopril and will continue to use it particularly in babies with a hypertensive left to right shunt. Patients who benefit usually do so on a low dose of the drug and currently the maximum dose we use is about 1·5 mg/kg/day. Ideally a double blind controlled trial is needed to prove the effectiveness of captopril in controlling heart failure in these circumstances but this poses many problems both practical and ethical. For example, a recent double blind trial of an alternative angiotensin converting enzyme inhibitor in adults was abandoned on ethical grounds as the patients receiving active treatment were doing so much better.[10] The major practical problem is that of finding a satisfactory objective measurement of improvement. Cardiac failure is a useful clinical term but a wide variety of pathological processes are involved and there is no universally agreed measurement of severity. A functional classification such as that of the New York Heart Association is often used in adult practice but could hardly be applied to infants.

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Artificial ventilation in severe pertussis

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SUMMARY A retrospective review was conducted of all children admitted to our intensive care unit over eight years with a diagnosis of pertussis that had been proved on culture. Altogether 789 children were seen as outpatients and inpatients. Twenty four of these children were admitted to the intensive care unit, 13 of whom required ventilatory support; two of the ventilated patients died. Intubation and ventilation were usually started for appreciable apnoea. Most patients requiring support were less than 3 months of age and required intervention within the first 16 days of cough. For these patients ventilation was neither difficult nor prolonged. Coughing spasms were not a problem and intubation and ventilation appeared to attenuate the progress of the disease. The presence of severe bacterial pneumonia associated with difficult ventilation requiring neuromuscular paralysis indicated a poor prognosis. It is suggested that intubation and ventilation can be safely used in very severe pertussis infection and, because of their greater risk of hypoxic damage and death, it should not be reserved as a last resort in critically ill infants.

Pertussis, a major cause of death in third world nations, continues to occur in Western countries because of breakdowns in immunisation.[1] Major outbreaks were reported from the United Kingdom in 1977–8 and 1982–3,[2] and in Oklahoma in 1983.[3] Pertussis often occurs in New South Wales despite an immunisation rate of more than 90%. Death from pertussis continues to occur in Western countries, because of respiratory failure, usually from apnoea rather than from secondary infection or aspiration. It is surprising that little has been written about the treatment of severe pertussis where ventilatory assistance is required.

Only one report discusses ventilation in children with pertussis.[4] This report suffers from a very low number of proved cases and no details of important aspects of ventilation. Most textbooks give no mention of intubation and ventilation except as a facility that must be available.[5-8] There is a common assumption that severe coughing spasms would make ventilatory intervention difficult and that such treatment should be avoided if at all possible. We therefore describe our experience from the intensive care unit of a referral teaching hospital with frequent admissions due to pertussis.

Patients and methods

A retrospective review was conducted of children admitted to the intensive care unit of the Children's Hospital, Camperdown, between January 1978 and March 1986 who had pertussis infection proved on culture. Children were admitted to the intensive care unit with this diagnosis if they were already receiving artificial ventilation or if appreciable apnoea or severe coughing spasms with cyanosis or bradycardia, or both, were present.

The following details were recorded on all patients: age, duration of hospital admission, changes seen on chest radiography, and complications. For ventilated patients the following details were also recorded: indications for tracheal intubation, time stage in the illness when ventilation was required, drugs used to facilitate artificial ventilation, ventilatory pressures required, and total duration of ventilatory assistance. These data were used to review the indications, efficacy, and complications of ventilatory assistance in pertussis.

Results

During the eight year and three month period of the study, there were 789 positive cultures for *Bordetella pertussis* in inpatients and outpatients seen at the hospital. Altogether 324 patients (41%) were admitted to hospital, 24 (7%) of them being admitted to the intensive care unit. Of these 24 children, 13 (54%) required ventilatory support, two (15%)

of the ventilated children died. Only those patients admitted to the intensive care unit are included in the analysis.

Indications for artificial ventilation were: (a) clinically important recurrent apnoea associated with bradycardia and cyanosis in 11 cases, (b) an episode of paroxysmal cough associated with periods of bradycardia over 40 minutes in one case; and (c) elective postoperative ventilation in one case.

Two ventilated patients were atypical and have been excluded from comparison with the non-ventilated group. The first, a 14 month old girl, had respiratory arrest associated with vomiting and aspiration and recovered without deficit after ventilation for one hour. The second, a 12 week old boy with biliary atresia was electively ventilated for 46 hours after a Kasai procedure for biliary atresia. His progress was complicated seven days postoperatively by wound dehiscence associated with paroxysmal cough but he had subsequent good recovery. One non-ventilated patient was atypical and has been excluded from comparison: this 10 month old infant presented with a clinical appearance consistent with viral bronchiolitis; both *B pertussis* and parainfluenza type III were isolated.

When these three patients are excluded, the average age of admission of the ventilated group was 5·5 weeks (3–11 weeks); the non-ventilated group had an average age of 8·2 weeks (4–14 weeks). The average duration of admission to hospital was 20·5 days (1–42 days) for the ventilated group and 24·2 days (2–70 days) for the non-ventilated group. On discharge, patients had only occasional mild coughing spasms.

All patients presented with typical symptoms of pertussis—that is, paroxysmal cough associated with cyanosis. In contrast to the ventilated group, only one non-ventilated patient had apnoea and only in a single episode. There were, however, no significant differences between the ventilated and non-ventilated groups in terms of duration of illness before admission to the ward, age, results of chest radiography, and duration of admission to the hospital. One ventilated patient had a history of prematurity and one had appreciable underlying heart disease. Apart from three patients further detailed below, chest radiography showed only overdistension of lung fields with or without areas of minor lung collapse.

Ventilation details in those patients requiring artificial ventilation are shown in the table. All patients were ventilated with a pressure-cycled ventilator. Patients were intubated on average at 7·3 days of cough (3–16 days). Duration of intubation was on average 139 hours (2–461 hours); average time of intermittent positive pressure ventilation was 107 hours (2–461 hours); average duration of subsequent continuous positive airways pressure was 32 hours (0–92). Eight patients were not difficult to ventilate. This group required only morphine infusion (20–40 µg/kg/hour) without neuromuscular paralysis and required only standard

Table *Details of children with pertussis requiring artificial ventilation*

Case No	*Age at intubation (weeks)*	*No of days illness when intubated*	*Duration of intubation (hours)*	*Ventilatory pressures (cm H_2O) peak/end-expiratory (maximum)*	*Duration of intermittent positive pressure ventilation (hours)*	*Duration of continuous positive pressure (hours)*	*Morphine (infusion or bolus)*	*Paralysis with pancuronium*	*Complications*
1	6	16	228	40/4	210	18	Infusion	+	Klebsiella pneumonia
2	4	3	174	26/6	126	48	Infusion		
3	3	10	123 5	25/5	49·5	74	Infusion		
4	11	7	24	38/4	24	—	—	+	Died
5	4	7	210	30/5	141	69	Infusion		
6	6	4	68	18/3	68	—	Bolus		
7	4	7	49	25/4	44	5	Bolus		
8	4	7	121	20/5	29	92	—		
9	6	3	2	Not available	2	—	—		
10	6	14	67	25/5	20	47	Infusion		
11	6	5	461	40/6	461	—	Infusion		Died/Klebsiella pneumonia
12*	60	8	9·75	Not available	1	—	—		
13*†	12	20	46·5	20/4	21	25·5	Infusion		
		27	21·5	18/4	16	5·5	Infusion		

*Excluded from comparison with non-ventilated patients
†Case 13 had two periods of ventilation

inflation pressures to produce normocarbia. After intubation, coughing spasms did not present a problem and there was a decrease in their severity and frequency. For this group, average time of intubation was 102 hours (2–210), average time of intermittent positive pressure ventilation was 60 hours (2–141); average time of continuous positive pressure airways pressure was 42 hours (0–92). Patients were weaned from ventilation when coughing spasms became infrequent and were not associated with apnoea, cyanosis, or bradycardia.

Three patients were difficult to ventilate, and two of them died. The first was a 6 week old boy whose course was complicated by collapse of his left lung and Klebsiella septicaemia. He was intubated for 220 hours with a maximum peak ventilator pressure of 40 cm H_2O, and a fractional inspiratory oxygen (FiO_2) up to 0·8. He received a morphine infusion and was paralysed with pancuronium for 111 hours. The second infant was an 11 week old girl who suffered a respiratory arrest before transfer to hospital; she deteriorated rapidly with severe pulmonary hypertension dying 24 hours after her arrest. Chest radiography showed overdistension and bilateral irregular dense opacities. Postmortem examination showed bilateral pertussis pneumonia. She had been ventilated for 24 hours from the time of respiratory arrest, with maximum settings of 38 cm H_2O, FiO_2 1·0. She received pancuronium for 9·5 hours. The third infant was a 6 week old girl with tricuspid atresia and compression of left mainstem bronchus. She required ventilation for 461 hours before she died with maximum settings of 40 cm H_2O FiO_2 1·0. Postmortem examination showed bilateral Klebsiella pneumonia.

All patients received erythromycin to reduce their infectivity. Corticosteroids were not used in any patient. No pathogens were isolated apart from those mentioned.

Discussion

In the United States, pertussis continues to decline as immunisation rates increase. In 1982, only 1895 cases were reported with four deaths; this is a similar mortality rate to that found in our study.[9] In Australia pertussis appears to be more frequent, this is possibly due to deletion of the 18 month pertussis vaccine from 1979; the vaccine has been recently reinstated because of increasingly frequent pertussis infection in preschool and school age children.

Pertussis remains a dangerous and potentially fatal disease, especially in the young infant.[10 11] Paroxysmal coughing, apnoea, and vomiting with aspiration may all lead to hypoxia and its sequelae. Pneumonia and lung collapse, though rare, are other potentially serious lung complications. Accurate death rate statistics are unavailable. Application of a statistical model to analysis of pertussis deaths in the United Kingdom suggested the death rate was probably twice to 10 times that reported on death certificates.[2] It is reasonable to assume that application of modern paediatric intensive care to seriously ill infants with pertussis could lower the death rate.

In our study the incidence of artificial ventilation may seem high. Children seen at this referral children's hospital, however, are a highly selected population, with a large number sent specifically because of the severity of their illness and the possible need for intensive care.

Supportive care remains the mainstay of treatment for pertussis. Specific treatments such as antibiotics, β agonists, and corticosteriods do not change the course of the disease.[9 12] Treatment consists of preventing serious hypoxia, and in hospitalised children oxygen is traditionally administered during coughing spasms with a means for ventilatory assistance (bag and mask) close at hand, but it is rarely needed.

In our experience, when the indications for ventilatory assistance applied in other serious respiratory illnesses of infancy are applied to pertussis, a number of infants with pertussis will require ventilatory assistance.

This study examined the results of tracheal intubation and ventilation of children with proved pertussis infection and we concluded that:

(1) Children requiring intervention are young (less than 3 months old with an average age of 5·5 weeks); intervention instituted for appreciable recurrent apnoea was required within the first 16 days of coughing.

(2) Mechanical ventilation is not difficult or prolonged in most patients. Only standard ventilatory pressures along with morphine infusion are required for control. Contrary to expectations, coughing spasms are not a problem. This may have been due to effective cough suppression by morphine infusion. It is our impression, however, that intubation and ventilation may attenuate the progress of the disease with a decrease in the frequency and severity of coughing spasms. The need to resort to neuromuscular paralysing agents was infrequent and associated with a poor prognosis.

(3) Infants requiring ventilatory support had more serious disease but do not have more

prolonged admissions to hospital than non-ventilated patients.

(4) Complications in ventilated patients are low and overall mortality is low, considering patient selection.

In our study, those patients who did not respond well to ventilation consisted of two children with Klebsiella pneumonia (one with a severe underlying cardiac disease) and another with severe intractable pulmonary hypertension. The last infant had effects from hypoxia secondary to respiratory arrest. It is evident that severe pneumonia associated with difficult ventilation requiring neuromuscular paralysis indicates a poor prognosis. It is of interest that acute viral bronchiolitis in infancy also has a higher death rate where there is pre-existing heart or lung disease.[13]

Despite the common assumption that artificial ventilation in pertussis should be avoided if possible, this report indicates that relatively early intervention in infants with respiratory failure due to pertussis infection is safe and should not be reserved as a last resort.

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Pulmonary function in children after neonatal meconium aspiration syndrome

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SUMMARY Eighteen children aged 6 to 11 years old who fulfilled criteria for the diagnosis of neonatal meconium aspiration syndrome were investigated to find out the prevalence of previous and current respiratory symptoms, and abnormal pulmonary function tests, chest radiographs, and ventilation scans. Eleven of the 18 had no respiratory symptoms and eight of these had normal pulmonary function on testing. Two had mild limitation of expiratory airflow that did not respond to treatment with bronchodilators, and one had exercise induced bronchospasm that responded to treatment with bronchodilators. Seven of the 18 had recurrent cough and wheezing compatible with a diagnosis of asthma, and five of these had appreciable exercise induced bronchospasm that responded to treatment with bronchodilators. None of the children with symptoms had a personal or family history of atopy or had had acute bronchiolitis. All chest radiographs were normal.

We found a much higher prevalence of asthmatic symptoms and abnormal bronchial reactivity among survivors of neonatal meconium aspiration syndrome than in the general childhood population. Aspiration of meconium may have long term consequences for the developing respiratory tract and is associated with abnormal respiratory function in later childhood.

Neonatal meconium aspiration results in respiratory distress of variable severity that is characterised by obstruction of airways, trapping of gas, inequality of ventilation and perfusion and a tendency to persistent fetal circulation About 10% of babies are born through amniotic liquor stained with meconium, and of these 20% develop clinical illness [1] Mortality is high, but among survivors the signs of respiratory distress seem to resolve completely. There has, however, been no study of the respiratory status of these children in later life. This is relevant because it is known that there are many respiratory illnesses in early life, both non-infectious and infectious, which appear to resolve but which are associated with impaired respiratory function in later years [2] There is also speculation that various insults to the developing respiratory tract in childhood may be determinants of chronic adult respiratory disease [3]

The aim of this study was to investigate respiratory symptoms and function after five years in children who had had severe respiratory distress caused by the neonatal meconium aspiration syndrome.

Methods

DIAGNOSTIC CRITERIA

Case records of infants born between 1975 and 1980 and admitted to three neonatal units and one regional paediatric intensive care unit in Liverpool were examined to find those with a diagnosis of neonatal meconium aspiration syndrome. Patients were accepted into the study if all the following criteria were met: (i) amniotic liquor stained with meconium was apparent before delivery; (ii) a paediatrician was present at delivery who performed direct laryngoscopy and retrieved meconium from below the vocal cords by endotracheal suction; (iii) respiratory distress was apparent immediately after birth; (iv) inspired oxygen of greater than 40% was required more than 48 hours; (v) there were radiological features of meconium aspiration syndrome; and (vi) other causes of respiratory distress—for example, pneumonia, lung malformation, and respiratory distress syndrome—had been excluded.

Details of all those who fulfilled these criteria were recorded, and the parents were contacted by letter inviting them to allow the child to take part in the study, and to attend the respiratory function laboratory for further evaluation.

RESPIRATORY SYMPTOMS

Parents and children who attended for further study completed a questionnaire about respiratory symptoms based on selected questions from the American Thoracic Society's Epidemiology Standardization Project.[4] This included questions about whether the child had recurrent coughs, phlegm, or wheezing; whether these symptoms were associated with upper respiratory tract infections or exercise; whether asthma had been diagnosed, and what drugs the child was taking. There were also questions about past respiratory illnesses (measles, bronchiolitis, pneumonia, pertussis, and croup), and about any history of atopy in parents or siblings (asthma, hayfever, or eczema). There were supplementary questions about the number of episodes of wheezing serious enough to cause shortness of breath in the previous 12 months, other health problems, and schooling. No attempt was made to assess the possible effects of environmental pollutants

PULMONARY FUNCTION TESTING

All pulmonary function tests were performed in the morning in the summer months June to September, and no child had had an upper respiratory tract infection within four weeks of testing. Functional residual capacity was measured by the helium dilution method,[5] using a PK Morgan multibreath closed circuit apparatus. After appropriate instruction and practise children performed maximal forced expirations into a turbine spirometer (Microloop, Micro Medical Ltd) linked to a microcomputer with visual display of the expiratory flow volume curve. The best of three forced expirations were used to record flow at 50% and 75% of forced vital capacity and the average flow between 25% and 75% of vital capacity. In addition, the volume expired in the first second of forced vital capacity and the forced vital capacity itself, were recorded from maximal expirations into a hand held electronic digital spirometer (pocket spirometer, Micro Medical Ltd). Peak expiratory flow rate was measured by a Wright peak flow meter.

As a test of exercise induced bronchospasm and response to treatment with bronchdilators, each child then undertook a free running exercise test lasting six minutes with measurements of peak expiratory flow rate at 0, 3, and 5 minutes of exercise, and at 3, 9, and 15 minutes after the end of the exercise. Salbutamol 200 μg was then inhaled by aerosol through a spacer device (Volumatic) and further peak expiratory measurements made five and 10 minutes later.

LUNG IMAGING

A plain posteroanterior chest radiograph was taken and each patient underwent 81m krypton ventilation scanning by steady state continuous tidal breathing.

Approval for the study was given by the hospital ethics committee.

ANALYSIS OF DATA

Measurements of peak expiratory flow from the exercise challenge were used to calculate the exercise induced bronchospasm index. This was calculated by the following formula: pre-exercise peak expiratory flow rate − minimum peak expiratory flow rate after exercise ÷ pre-exercise peak expiratory flow rate ×100%. The % response to bronchodilators was calculated from: maximum post-bronchodilator peak expiratory flow rate − peak expiratory flow rate at 15 minutes post-exercise ÷ maximum post-bronchodilator peak expiratory flow rate ×100%.

Pulmonary function test values were expressed as % predicted for height and sex.[6 7] Individual test values were considered abnormal if they were more than two standard deviations below the mean for composite reference values,[6] or below the normal (lower) 95th centile for maximal expiratory flow volume curve reference values.[7] For the exercise test, an exercise induced bronchospasm index of greater than 10%,[8] and a bronchodilator response of greater than 15% were considered abnormal.

Radiographs and 81m krypton ventilation scans were reported independently by a radiologist not taking part in the study.

Results

During the six year period 72 neonates were diagnosed in their medical records as having 'meconium aspiration syndrome'. Only 34 of these, however, fulfilled the strict criteria outlined for this study.

Six of the 34 died, all had received mechanical ventilation and they all died from birth asphyxia or severe meconium aspiration, or both. Of the remaining 28 children, 10 families had moved from the address given at the time of the child's birth, but four of these were traced and completed the questionnaire by post or telephone. Thus 18 children attended for testing of pulmonary function. Neonatal details of those children who did not attend for pulmonary function testing (n=10) did

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not differ significantly from those of the ones who were tested (n=18) The table summarises the neonatal details of the 18 children studied. Two babies had received full mechanical ventilation and four others had developed pneumomediastinum and pneumothorax.

At follow up the mean age was 7·8 years (range 5·7–11·2) and all except one was of normal height (mean height standard deviation score = −0·12, range +1·24 to −3·1).

RESPIRATORY SYMPTOMS

Eleven children were completely healthy without any current or previous respiratory symptoms. Seven children had recurrent coughs and wheezing associated with upper respiratory tract infections of whom six also experienced coughs and wheezing at times other than during infections or during exercise. Five of these seven had had more than two episodes of wheezing serious enough to cause shortness of breath in the previous 12 months. These seven symptomatic children had no family history of atopy and none had had acute bronchiolitis; one had had croup. In this group two families were aware that their child had 'recurrent bronchitis' and two had been diagnosed as having asthma and treated by their family doctor.

Table *Neonatal details of 18 children followed up five years after having had meconium aspiration syndrome*

	Mean	*Range*
Gestation (weeks)	40·3	38–42
Birthweight (g)	3550	2620–4250
Maximum fractional inspired oxygen concentration	0·5	0·4–1
Duration of oxygen requirement (hours)	90	48–192
Apgar score		
at 1 minute	4·5	1–8
at 5 minutes	7·2	1–10
at 10 minutes	8·1	5–9

Of the 11 asymptomatic children, four had a family history of atopy, two had had croup, and one had had acute bronchiolitis

Thus, seven of 18 survivors of meconium aspiration syndrome had recurrent symptoms compatible with asthma, and this was not explained by a family history of atopy, or a history of respiratory illness after the neonatal period.

PULMONARY FUNCTION TESTS

The results of each child's tests are shown in figs 1, 2, and 3, and compared with the normal reference ranges.[6 7]

SYMPTOMATIC GROUP

Among the seven symptomatic children, two had normal pulmonary function tests both at rest and after exercise. The remaining five all had appreciable bronchoconstriction when they exercised and

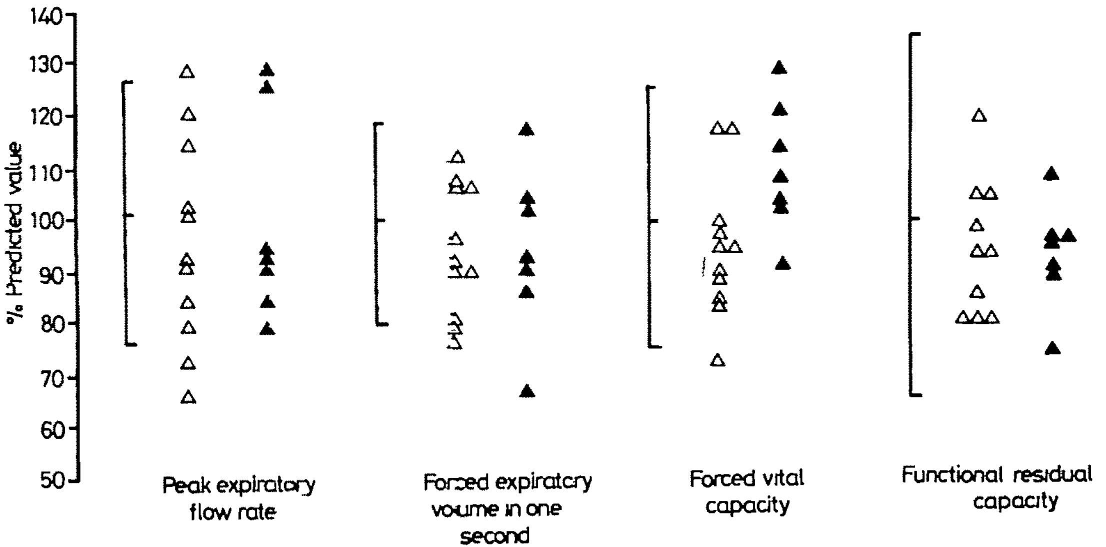

Fig 1 *Peak expiratory flow rate, forced expiratory volume in one second, forced vital capacity, and functional residual capacity in 18 children who had had neonatal meconium aspiration syndrome, shown as % predicted; normal ranges for each test indicated by bars.[6] ▲ = symptomatic children and △ = asymptomatic children.*

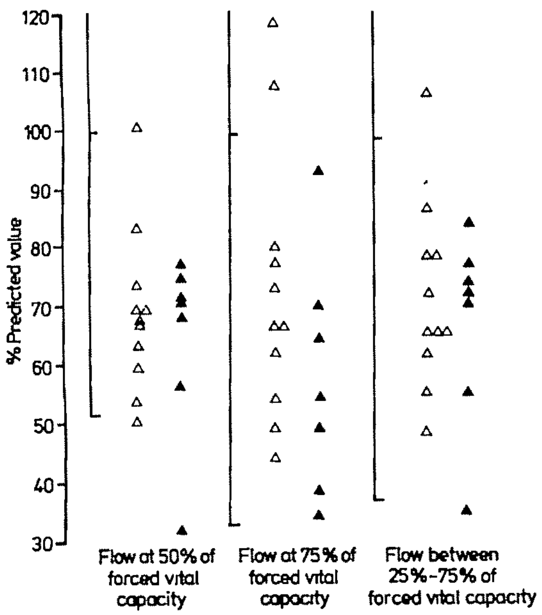

Fig 2 *Flow at 50% forced vital capacity, flow at 75% forced vital capacity, and flow between 25% and 75% of forced vital capacity in 18 children who had had neonatal meconium aspiration syndrome, shown as % predicted, normal ranges and lower 95th centile are indicated by bars.*[7] *▲=symptomatic children and △=asymptomatic children*

all responded to treatment with bronchodilators. One child who was known to be asthmatic had low forced expiratory volume at one second, low flow at 50% of forced vital capacity, and low flow between 25 and 75% of vital capacity at rest. This patient and one other who responded to treatment with bronchodilators had abnormal ventilation scans that showed moderate generalised decreased air entry to the left lung. All the chest radiographs were normal.

ASYMPTOMATIC GROUP

Among the 11 asymptomatic children, eight had normal pulmonary function both at rest and after exercise. One child had significant exercise induced bronchospasm (20% fall), and responded to treatment with bronchodilators (16% rise). The remaining two children had low peak expiratory flow rate, low forced expiratory volume at one second, and low flow at 50% of vital capacity that did not vary with exercise or respond to inhaled bronchodilators.

All chest radiographs and ventilation scans were normal in this group

Ten of the 18 survivors (56%) of meconium aspiration syndrome had normal pulmonary function tests. Six of the 18 (33%) had abnormal bronchial reactivity.

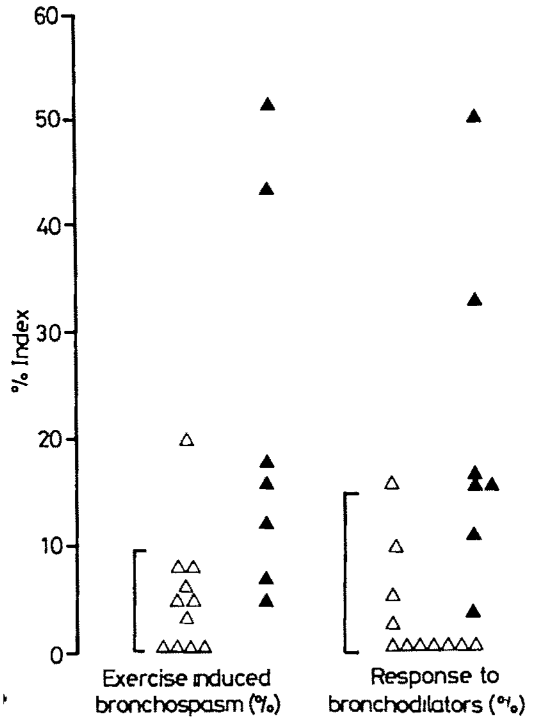

Fig 3 *Exercise induced bronchospasm index (%) and response to treatment with bronchodilators (%) in 18 children who had had neonatal meconium aspiration syndrome Ranges and upper limit of normal are indicated by bars*[8] *▲=symptomatic children and △ asymptomatic children.*

The severity of the neonatal meconium aspiration syndrome did not seem to correlate with the presence of symptoms or abnormal pulmonary function. The two children who received mechanical ventilation for meconium aspiration syndrome were symptomatic, but neither had abnormalities of pulmonary function at rest or after exercise.

Discussion

We found a high prevalence of asthmatic symptoms (39%) and abnormal bronchial reactivity to exercise (33%) among survivors of neonatal meconium aspiration syndrome This is much higher than the estimated prevalence of 10–12% in the general childhood population at this age.[9] [10] These children were not atopic or from atopic families, and with one exception (croup) had not suffered any other respiratory insult known to be associated with bronchial reactivity in later childhood. The failure to diagnose asthma among the symptomatic children in our study was comparable with that found in larger community studies.[9] [10]

By our inclusion criteria for diagnosing meconium aspiration syndrome we probably excluded the milder forms of the disease, hence the findings of this study apply only to moderate and severe meconium aspiration syndrome. We were only able to test fully 18 of the 28 surviving children initially identified as having serious neonatal meconium aspiration syndrome. The effect of selection bias on our findings must therefore be considered Six families could not be traced because they had moved from our region and can therefore legitimately be excluded from analysis. Four children declined to attend for pulmonary function testing but answered the respiratory symptom questionnaire; three were asymptomatic but one had recurrent bronchitis' with symptoms of recurrent cough, wheezing and breathlessness, and used bronchodilators occasionally. Thus it would not seem that there was selection bias. Furthermore, even if all children had been fully evaluated the group would still contain larger numbers of children with asthmatic symptoms and bronchial reactivity than the general population; hence the main conclusion of the study would be unchanged

Among the 11 asymptomatic children there were two who had evidence of mild fixed obstructive airways disease on pulmonary function testing, with limitation of expiratory airflow at various lung volumes. All the other children had test values within normal limits, but tended towards the lower limit of normal (fig 2).

Our findings of abnormal bronchial reactivity to exercise and mild expiratory airflow limitation makes neonatal meconium aspiration syndrome another factor in the wide range of insults to the developing respiratory tract that may cause abnormalities of pulmonary function in later life Aspiration of other foreign material (such as hydrocarbons[11] or fresh water[12]) is associated with later abnormalities of pulmonary function, especially abnormal bronchial reactivity, long after symptoms have resolved.

It seems likely that the developing respiratory tract is vulnerable to damage by many insults, and the non-specific response is abnormal bronchial reactivity and limitation of airflow.[13]

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Teenage sexual intercourse and pregnancy

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SUMMARY One hundred and one pregnant girls aged under 18 years were interviewed to collect information about the development of their sexual awareness, attitudes towards relationships, and about their social context. The data show that the girls were likely to come from homes where the parents were divorced, where the mother married when she was under 21 years of age, and where her first child was conceived out of wedlock. Altogether 76 of these pregnant girls first had intercourse before they were 16 years old. The younger the girl at first intercourse the sooner it occurred in the relationship and for almost half of the girls first intercourse was unplanned. Although almost half used contraception on the first occasion, only one third of the girls used contraceptives regularly. Most expressed the wish that they had delayed intercourse until they were older.

In 1984 in England and Wales there were just under 10 000 conceptions to girls under 16 years of age, of which roughly half were terminated. The conception rate fell in the late 1970s but rose again so that by 1984 (8·4 per 1000) it had almost reached the 1974 level (8·5 per 1000).[1] Girls who continue with their pregnancy are at increased risk of hypertension and eclampsia, and the perinatal mortality is highest among girls under 16 years of age.[2] Teenage mothering also carries risks for the offspring including a high infant mortality rate[2 3] and increased morbidity in terms of hospital admissions, trauma, and school performance.[4 5] Young mothers often suffer educational deprivation, social isolation, and financial hardship. Those girls who have their pregnancy terminated are able to continue with their education, but there is a risk of cervical incompetence after termination particularly when performed on young teenage girls [2 6 7] Termination may adversely affect the outcome of future pregnancies and can also have appreciable psychological consequences for the girl.[7 8]

Cervical carcinoma, which is increasing in incidence and presenting at a younger age, is directly linked to the age of first intercourse and to the number of partners,[2] and the spread of infection by human immunodeficiency virus (HIV) is also linked to the number of sexual partners. These medical problems emphasise the risks associated with teenage intercourse, particularly if with a number of partners, in addition to the risks of the pregnancy itself.

Sex education has increasingly been included in the school curriculum and in some schools there has been a growth in social education with an emphasis upon personal relationships and social skills. Reid has stated that 'the aims of sex education and related courses for the 14–16 age group may well include the prevention of unwanted pregnancies. However, this is often neither explicit or even uppermost in teachers' minds.'[9] School sex education curricula may not emphasise responsibilities associated with close relationships or the possibility of delaying first intercourse. Despite the considerable adverse effects of pregnancy on both the girl and any offspring few data are available, in the United Kingdom, on the circumstances of teenage sexual intercourse and conception Three studies have reported the sociological aspects of teenage pregnancy as seen in large multiracial urban conurbations [10–12]

This study was undertaken in a health district containing a small city and which has a stable indigenous and semirural population. The study has provided data, unbiased by major religious or ethnic differences, on the family background of young pregnant teenage girls, their relationships with the opposite sex, and the knowledge that they gained from sex education. Behavioural and educational aspects were of particular interest in the study in order to identify important areas for sex education programmes and to inform professionals concerned in the care of children about the context of sexual activity in teenagers.

This study was approved by the district ethical committee.

Methods

All pregnant girls under 18 years admitted to hospital were identified either from the delivery record book on the labour ward or by the nursing staff on the postnatal and gynaecological wards. Altogether 108 girls were selected on the basis of the availability of the interviewer, and they are representative of all such admissions Sixty six had delivered a baby and 42 had had a termination; however, seven of those who had had a termination refused to be interviewed

Thirty six primagravidae, aged between 20–25 years, were also interviewed as a comparison population of girls who had not become pregnant before the age of 20. The girls were interviewed privately (for roughly one to two hours) while in hospital by the same interviewer (HAC).

Each interview was conducted using a questionnaire but with an opportunity for open discussion and verbatim responses, which were encoded subsequently. The areas on which there were detailed questions included the girl's family background, her school background, degree of parental supervision, sex education received from home, school, and friends, personal relationships, and factors surrounding first intercourse and the pregnancy itself.

There were four discussion sections. The first on how sex education in schools could be improved, the second concerned the way the girl saw her future, the third information she wished she had received, and the fourth what advice she would give to a younger sibling or friend.

To assess the significance of factors in the various tables presented, contingency-table analysis and log-linear modelling were used. These analyses provided the χ^2 values from which the significant p values were obtained.

Statistical Discriminant Analysis was used to identify the important demographic factors that best distinguished between the study and comparison groups (for the mathematical and statistical details of the technique see, for example, Johnson and Wichern[13]). The particular method used entailed a stepwise procedure in which only those variables contributing significantly to the discrimination were included in the estimated discriminant function.

Results

Out of the 101 girls interviewed 13 had already experienced pregnancy, five of these had ended in termination, one in a miscarriage, and seven had delivered a baby. Forty one of the study group had conceived before their 16th birthday.

FAMILY BACKGROUND

Table 1 shows that the social class distribution (based upon the Registrar General's Classification of the girl's father's occupation) was similar in both the study and the comparison group. In particular, in the study group, there was no evidence of bias towards the lower social classes. A comparison of

Table 1 *Family background of girls studied*

	Study group No (%)			*Comparison group No (%)*
	Delivery	*Termination*	*Total*	
	n=64	*n=34*	*n=98*	*n=35*
No from families with ⩾3 children	27 (42)	11 (32)	38 (39)	12 (34)
Social class.	*n=61*	*n=35*	*n=96*	*n=36*
Ia, II	8 (13)	15 (43)	23 (24)	5 (14)
III non-manual	7 (11)	5 (14)	12 (13)	4 (11)
III manual	19 (31)	8 (23)	27 (28)	14 (39)
IV, V	7 (11)	1 (3)	8 (8)	3 (8)
Unemployed	6 (10)	3 (9)	9 (9)	3 (8)
Unclassified	14 (23)	3 (9)	17 (18)	7 (19)
	n=66	*n=35*	*n=101*	*n=36*
Parents divorced	32 (48)	14 (40)	46 (46)	9 (25)
	n=60	*n=34*	*n=94*	*n=33*
Mother married when under 21 years	45 (75)	18 (53)	63 (67)	12 (36)
	n=65	*n=34*	*n=99*	*n=36*
Mother's first child conceived out of wedlock	36 (55)	14 (41)	50 (50)	7 (19)

*Study group total significantly different than the comparison group ($p<0.05$)
n=Number with data for this question.

the group who had had a termination with those girls in the study group who had delivered a baby, however, showed a significant difference, with more of the group who had had a termination coming from the non-manual sector (p<0·025). The measure of family size used in table 1 included step brothers and sisters and half brothers and sisters and it indicated that the girls in the study group did not come from unusually large families. The parents of the study group were significantly more likely to be divorced, the mothers to have married when they were aged under 21 years, and the first child in the family to have been conceived before marriage.

Ten (10%) of the girls in the study group did not get on with their mother and a quarter did not get on with their fathers; in the comparison group four (11%) did not get on with either parent.

With regards to supervision exercised by the girl's parents in both study and comparison groups (table 2) the girls who first had intercourse under 16 years were less likely to have to ask permission to go out than those who were over 16 years old. Similarly the girls who were under 16 years at first intercourse were less likely to have been given a time at which they had to be home. Most of the parents knew where their daughters were going, in both the study and comparison groups.

Table 2 *Supervision exercised by parents*

	Study group No (%)		*Comparison group No (%)*	
Age at first intercourse	<16	≥16	<16	≥16
Permission needed to go out	*n=76* 49 (64)	*n=24* 22 (92)*	*n=6* 3 (50)	*n=30* 24 (80)*
Time given to be home by	57 (75)	22 (92)*	*n=7* 4 (57)	*n=29* 23 (79)*
Limit given to number of times out	21 (28)	8 (33)	1 (14)	10 (35)
Parents who wait up/stay awake	55 (72)	15 (62)	3 (43)	24 (83)*
Parents who know where daughter is going	*n=75* 64 (85)	23 (96)	6 (86)	26 (90)
Parents who comment on dress	19 (25)	*n=23* 7 (30)	2 (29)	10 (34)

*Significant difference from <16 group (p<0·05).
n=Number with data for this question

Table 3 *Age at first intercourse*

	Study group No (%)	*Comparison group No (%)*
Age at first intercourse (years)	*n=100*	*n=36*
≤14	32 (32)	2 (6)
15	44 (44)	5 (14)
16, 17	24 (24)	12 (33)
>17	*	17 (47)

*Girls in study group were all under 18
n=Number with data for this question

DEVELOPMENT

In the study group menarche started significantly earlier; 64 (63%) starting their periods before they were 13 years old in contrast to 14 (39%) of the comparison group (p<0·05). A third of the girls in the study group started having intercourse before their 15th birthday and three quarters before their 16th (table 3) In the comparison group one fifth had started having intercourse before the age of consent but had not become pregnant.

Table 4 shows that in both the comparison and study groups the younger the girl at first intercourse the sooner this occurred in the relationship. Considering the study group alone, we can see that this trend continues even down to the lowest age group and the shortest relationship, although this does not achieve significance. Combining the groups shows that those girls having first intercourse under 16 were more likely to have intercourse early in a relationship (less than 6 months) than those beginning over 16 (p<0·05).

Of those who started having intercourse when they were under 16 years only a quarter said they

Table 4 *Age and length of relationship before first intercourse*

	Age at first intercourse				
	Study group No (%)			*Comparison group No (%)*	
	≤14	*15*	*≥16*	*<16*	*≥16*
Length of relationship before intercourse (months)	*n=30*	*n=44*	*n=24*	*n=7*	*n=29*
0–3	14 (46)	17 (39)	8 (33)	5 (71)	9 (31)
4–6	8 (27)	13 (29)	5 (21)	0	4 (14)
>6	8 (27)	14 (32)	11 (46)	2 (29)	16 (55)

n=Number with data for this question

had enjoyed intercourse on the first occasion and although half of those over 16 had enjoyed their first experience of intercourse it is of interest that even in the older group one half had not enjoyed the experience. There were no significant differences between those who were under and those over 16 years at first intercourse in relation to whether the first occasion of intercourse was the beginning of a relationship with intermittent or regular intercourse. For both age groups the number of girls who continued to have intercourse with their first sexual partner were significantly less in the study group than in the comparison group (p<0·01). As expected, boyfriends were older, with a third of girls in both the study and the comparison group having boyfriends who were four or more years their senior. Despite this only 17 of the study group felt that they had been pressurised by their partners into having intercourse (table 5) and this was not related to the age of the boyfriend. A third of the study group had planned to have intercourse on the first occasion, but almost half claimed it was unexpected and had 'just happened'. In the comparison group it was more likely that the first occasion of intercourse had been a conscious decision (p<0·05) but it was still unplanned in a quarter of cases and unwanted in a tenth.

Of the 35 girls in the study group who were asked, 20 thought their parents were aware that they were having intercourse with their boyfriend before conception took place. Fifty three of the 90 girls asked in the study group (59%) had intercourse for the first time in either their or their boyfriend's parent's home, and in just over a fifth of these cases the parents were actually at home. This contrasts with nine out of 25 (36%) of the comparison group who had intercourse on the first occasion in their parent's homes. In most of the remaining cases in both groups intercourse occurred while the young people were away from parental homes and in only a very few cases (6%) was first intercourse associated with a party or alcohol consumption. A third of the girls in the study group who had started intercourse under 16 years of age had had three or more partners by the time of the interview (table 6). In the comparison group, where the women were on average seven years older, six out of seven girls who first had intercourse under 16 years had had at least three partners.

Table 5 *Reasons given for first intercourse*

	Study group No (%)	*Comparison group No (%)*
Reason given for first intercourse	*n=101*	*n=36*
Conscious decision	33 (33)	19 (53)
'Just happened'	45 (45)	9 (25)
Pressure from boyfriend	17 (17)	4 (11)
Other—for example, uncertain	5 (6)	4 (11)

CONTRACEPTIVE USAGE

Forty six of the girls in the study group aged under 16 years at first intercourse used contraception on the first occasion, and only a quarter used contraceptives on a regular basis (table 7); in all cases the contraceptive method used was the sheath. The comparison group was significantly more likely to have used contraceptives on the first occasion and to have continued to do so whether or not they were under 16 years at the time of first intercourse. Although a quarter of the comparison group and just under half of the study group said intercourse had just happened, almost a half of these girls reported that their boyfriends had used contraception, indicating that their partners, at least, had anticipated having sexual intercourse.

Twenty two (61%) of the comparison group compared with only 15 (15%) of the study group (excluding terminations) had planned the pregnancy

Table 6 *Number of partners up to interview according to age at first intercourse*

	Age at first intercourse			
	Study group No (%)		*Comparison group No (%)*	
	<16	*≥16*	*<16*	*≥16*
Number of partners	*n=76*	*n=23*	*n=7*	*n=29*
[illegible]	40 (53)	16 (70)	1 (14)	14 (48)
[illegible]	13 (17)	3 (13)	0	5 (17)
≥[illegible]	23 (30)	4 (17)	6 (86)	10 (34)

n=Number with data for this question

Table 7 *Use of contraceptives according to age at first intercourse*

	Age at first intercourse			
	Study group No (%)		*Comparison group No (%)*	
	<16	*≥16*	*<16*	*≥16*
Contraceptive used on first occasion*	*n=76* 35 (46)	*n=24* 15 (62)	*n=7* 6 (86)	*n=29* 24 (83)
Contraceptive always used*	18 (24)	12 (50)	5 (71)	18 (62)

*Study and comparison groups significantly different (p<0 01)
n=Number with data for this question.

Six of the latter had already had one child, of which two had been placed for adoption, four had had their first child at 14 or 15 years of age and wanted their next child within two years, and one girl had married before conception. Of those with unplanned pregnancies, most had not used contraception at the time that they conceived (table 8). Contraception was used unsuccessfully in a significant proportion of both the study and comparison groups.

Ten of the girls had been undecided whether the babies would be adopted after the pregnancy, but after the delivery most decided to keep them. Ethical committee approval was not sought for any follow up of the girls and therefore the number of babies that were finally adopted is unknown.

REGRETS

In the study group of those who had had more than one partner half definitely regretted this and a third had some regrets but felt it was all part of a learning process; a third of the comparison group also had definite regrets at the number of partners that they had had. Most of the study group felt they had been too young when they first had intercourse and wished they had delayed intimate sexual activity until they were older.

DISCRIMINANT ANALYSIS

Discriminant analysis identified the three main variables that best discriminated between the study and comparison groups, and it provided confirmation of our initial analyses. These variables were: girl's mother divorced, mother's own first child born out of wedlock, and early menarche. The estimated discriminant function can be used to form the basis of a classification analysis for any new cases, and as a check on the adequacy of the derived function the original cases (that is, the data from the study and comparison groups) can be classified to see how many are correctly allocated by the variables defined in the function. In our analysis roughly 70% of the original cases were correctly classified to their group

Table 8 *Reason given for conception*

	Study group No (%)		*Comparison group*
	Delivery	*Termination*	*No (%)*
	n=66	*n=34*	*n=36*
Planned pregnancy*	10 (15)	0	22 (61)
Unplanned pregnancy*	*n=56*	*n=34*	*n=14*
No contraceptive used	43 (77)	23 (68)	9 (64)
Contraceptive used unsuccessfully	12 (21)	11 (32)	4 (29)
Other reasons	1 (2)	0	1 (7)

*Delivery and termination subgroups and the combined study group were all significantly different from comparison group (p<0 01).
n=Number with data for this question

Discussion

In contrast to much of the published data on teenage pregnancy, this study has been undertaken in what is considered to be a privileged part of rural England where inner city deprivation and delinquency are quantitatively less and the effect of ethnic and religious variables are largely insignificant. The rate of teenage conception to girls under 16 years of age for the South West (7·6 per 1000) is, however, similar to the national average (8·6 per 1000).[1] The lack of variation in the local population makes interpretation of the data simpler and may also make any health education initiatives easier to initiate.

The problem of selecting a suitable set of 'controls' for comparison with the study group was difficult, as it was not felt to be ethical to ask specific sexual questions of teenagers who might not yet be sexually active. The comparison population is one which consists of women who have avoided what we hypothesised to be a disadvantage: that of becoming pregnant while a teenager. The sample is further biased by not including women experiencing a first pregnancy for which they requested termination. These constraints upon the sample selection may have accentuated differences between the study group and the comparison group, the members of which are on average seven years older than those in the study group and memory of their teenage years is likely to be both less accurate and to some extent biased by subsequent experience. The data thus provide a useful comparison rather than a control population.

The previously reported excess of families of lower socioeconomic state with large numbers of children has not been found in these data.[10 11 12 14] There were no significant differences between the social class distribution of the pregnant teenagers and either the comparison group or the local population, but there was a significant difference within the study group, with more of those who were having terminations coming from the non-manual sector. An explanation for this could be that those from the lower social classes are more accepting of the pregnancy whereas for those from the higher social classes the pregnancy would be viewed as causing disruption to both the family and, importantly, to the girl's education. The size of the families is similar for the study and comparison groups and in particular there was no excess of large families (five or more children) as has been previously reported.[9 11 12 14]

A significantly greater number of the pregnant girls' mothers were divorced or separated, had had their own first child conceived out of wedlock, and had married young, giving weight to the hypothesis that a 'cycle of disadvantage' argument applies to these girls. In almost 90% of cases in the study group and 40% in the comparison group the pregnancy had been the unplanned result of a sexual relationship.

The fact that intercourse occurred most often in a parental home suggests that parents were aware, or were in a position to guess, that intercourse was likely. This is supported by the fact that a relatively high proportion of the girls who were asked thought that their parents were aware that they were having intercourse with their boyfriend.

Most of the study group and a quarter of the comparison group claimed that they had been unprepared for the possibility of intercourse and had not been made aware of the possible disadvantages. Clearly, the event was more often planned by their partners as half of them had available and made use of contraceptives on this first occasion.

Nearly four fifths of the girls pregnant before their 18th birthday had had intercourse before their 16th birthday, and one fifth of the comparison group who had avoided pregnancy had also had first intercourse before they were 16 years of age. The comparison group was drawn from a population five times larger than that from which the study group was drawn, therefore, it can be extrapolated that a significant proportion of teenagers are sexually active in their midteens and before the age of consent. The data suggest that girls who mature physically early are at greater risk of unplanned intercourse and pregnancy. Not only has this been previously reported,[15] but a rational explanation can be proposed. The psychological maturation of the girl is unlikely to match her physical development and she will be attractive to older boys while at an age where she is less able to resist personal and peer pressure. Boyfriends tended, as expected, to be older than the girls, but while there was no greater age differential in years for the younger girls we suggest that the difference between a 14 and 18 year old are greater than between a 17 and 21 year old. Younger girls were more likely to have intercourse earlier in their relationships, a possible explanation being that a 14 year old regards a two to three month relationship as serious where for the older girl this definition may not be used until the relationship has lasted for six or more months. Having had a relationship involving intercourse most girls had intercourse with subsequent partners, particularly those girls younger at first intercourse in both the study and comparison groups.

Previous work has concentrated on describing the characteristics of pregnant teenagers and Wilson attempted to develop scores to identify high risk populations.[11 14] In this study though there are sociological and physical demographic characteristics that distinguish them as a group from the general population, the pregnant teenagers are not separable from the general population with any degree of specificity or precision. In our data the process would result in a large target group that would contain only about two thirds of those likely to become pregnant.

A substantial proportion of girls in their midteens are sexually active and at risk of becoming pregnant, and this may be relatively greater in those from particular family backgrounds and those who begin such relationships in their early teens.

Sexual intercourse between teenagers is often justified as being appropriate behaviour in a 'stable relationship'.[16] The girls, by their own report, said first intercourse was more likely to happen in default of any considered merit or demerit than as a planned progression of a serious relationship. Once having experienced a relationship with intercourse (and despite the fact that the first occasion of intercourse is often reported as not enjoyable) girls are likely to be sexually active with subsequent partners and this happens earlier in these later relationships.

Early teenage intercourse exposes the girls to risks not only of pregnancy, but also to those areas of medical concern associated with multiple partners—namely, sexually transmitted diseases, infertility and cervical carcinoma. We, therefore, suggest there needs to be a radical reappraisal of sex education in school, which in the past has mainly been to inform as to biology and physiology of reproduction and only more recently to inform as to the avoidance of unplanned pregnancy and, in a few instances, to discuss the responsibilities of relationships and parenthood. There is a good medical case to include the avoidance of early intercourse. This is further supported by the fact that most wished they had delayed first intercourse until they were older and that 80% of the study group who had had more than one partner had some regrets and even in the comparison group one third regretted having had multiple partners.

The data from our research suggest that at least one in five teenage girls are sexually active before the age of consent. Paediatricians need to be aware of this possibility when prescribing because of potential drug interactions, for counselling of girls with chronic illness, and for diagnosis. At least a substantial minority of girls in their midteens expose themselves to risks associated with teenage intercourse, multiple partners, and pregnancy, each of which they may later regret.

We suggest that there should be a much greater emphasis on personal relationships and the implications of intercourse in these relationships in the content of health and sex education material in schools and by the media.

Further information is needed about the teenage population as a whole and studies are in progress in this area.

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Parental diary of infant cry and fuss behaviour

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SUMMARY Despite their common use parental diaries of infants' cry and fuss behaviour have not been compared with objective methods of recording. To understand what is meant by the descriptions of crying and fussing in the diaries, the diaries of 10 mothers of 6 week old infants were compared with tape recordings of vocalisations made by the babies over a 24 hour period. There were moderately strong correlations between the frequency of episodes (clusters of 'negative vocalisations') on the audiotape and episodes of 'crying and fussing' in the diaries, and between the duration of episodes on the audiotape and episodes of 'crying' in the diaries. To assess the acceptability of the diaries for recording information for clinical and epidemiological research, they were then used in a population study of a wide socioeconomic group. Usable data were obtained from 91% of the sample. The results suggest that despite pronounced differences between recording methods, these diaries may provide valid and useful reports of crying and fussing in the short term.

Parental recording has commonly been used to describe emerging patterns of infant behaviour, and has a potential for use in the clinical assessment of behavioural problems. Most of our knowledge about infants' crying after the neonatal period is derived from studies that used diaries, despite the recognised potential of over or under reporting.[1–4] Data from diaries,[1–4] tape recordings,[5] parental recall,[6] and direct observations[7] have all shown that the amount of crying tends to increase until about 6 weeks of age and then gradually decreases, and that within a 24 hour period crying occurs more often in the evening; this implies that diary reporting is reasonably accurate. We are not aware, however, of any data that directly compare parental recordings with a recording system less susceptible to bias. As a result, we know little about how parent recording represents the infant vocalisations which are part of the crying behaviour.

The diaries used in this study were designed to be easy to use and to be suitable for a diverse sample of the population. We first compared them with 24 hour audiotape recordings of the infants' vocalisations. Crying refers to a complex act that includes elements of movement, facial expression, and voice, and is usually interpreted as expressing a negative emotion. In the tape recordings the vocal part of crying is designated as negative vocalisation compared with neutral sounds (such as grunting) and positive sounds (such as cooing).

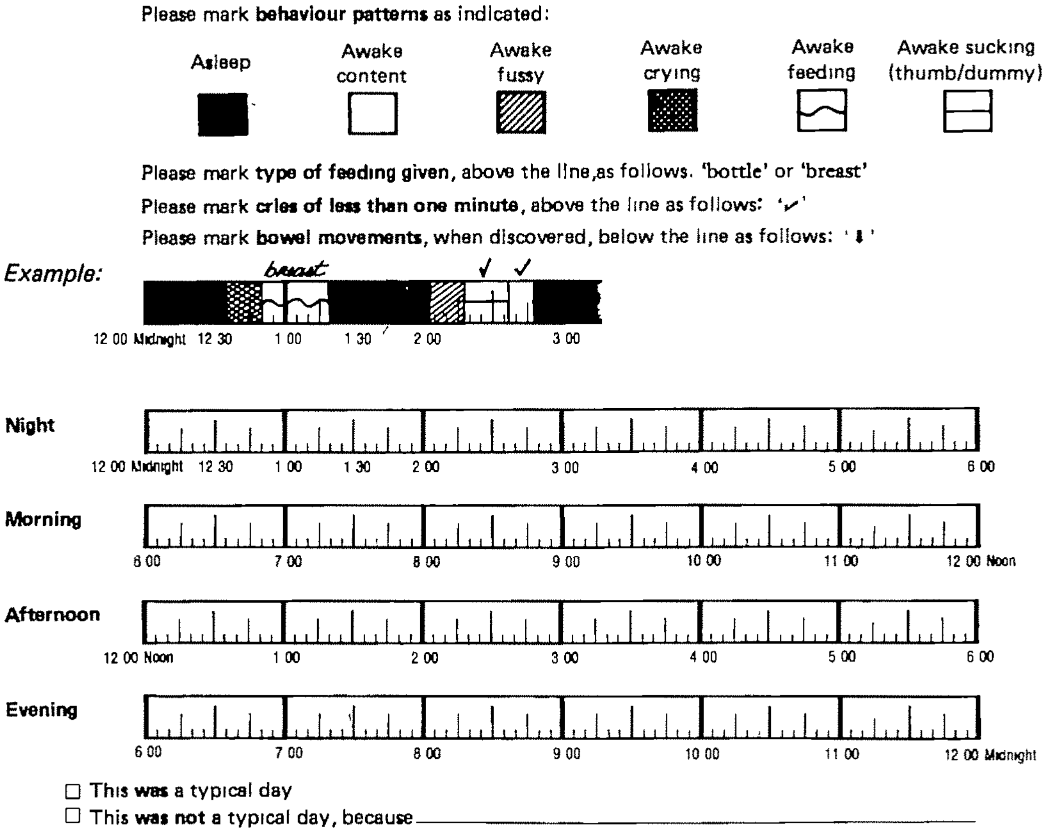
Secondly, the sociodemographic characteristics of parents who returned diaries with readable data were compared with those of parents who did not from a population sample in a prospective cohort study. Thus the findings describe quantitative associations between negative vocalisations and the diary records of crying and fussing, they illustrate the limitations of both techniques in assessing the amount of infant crying, and they indicate the potential limits on the use of diaries for this purpose in the general population.

Subjects and methods

Ten mothers (who spoke fluent English or French) of normal 6 week old infants, who were in the nursery of a large general hospital associated with the university or a community health unit volunteered to take part in the comparison of diaries and tape recordings. The mean age of the infants was 6·3 weeks (range 5·5–7) at the time of recording, there were five boys and five girls, and seven were exclusively breast fed. The mean (SD) socioeconomic score measured by Green's two factor index[8] was 67·8 (11·7), a wide range that is typical of this community.[9] Informed consent was obtained before the tape recordings were made.

PARENTAL DIARIES

Fig 1 shows the format of the diaries; this was the



Please mark **behaviour patterns** as indicated:

Asleep
Awake content
Awake fussy
Awake crying
Awake feeding
Awake sucking (thumb/dummy)

Please mark **type of feeding given**, above the line,as follows. 'bottle' or 'breast'

Please mark **cries of less than one minute**, above the line as follows: '✓'

Please mark **bowel movements**, when discovered, below the line as follows: '⬇'

Example:
breast
✓ ✓
12 00 Midnight 12 30 1 00 1 30 2 00 3 00
Night
12 00 Midnight 12 30 1 00 1 30 2 00 3 00 4 00 5 00 6 00
Morning
6 00 7 00 8 00 9 00 10 00 11 00 12 00 Noon
Afternoon
12 00 Noon 1 00 2 00 3 00 4 00 5 00 6 00
Evening
6 00 7 00 8 00 9 00 10 00 11 00 12 00 Midnight

☐ This **was** a typical day

☐ This **was not** a typical day, because ______

Fig 1 *Example of diary; Four 'time rulers' each representing six hours are included on each page and vertical lines indicate five minute intervals*

result of extensive pilot studies among mothers of normal children. 'Time rulers' were filled in using symbols representing six behaviour patterns—sleeping, awake and content, fussing, crying, feeding, and sucking. The smallest unit of time that could be recorded was five minutes. To make them easy to use the symbols were designed to have definite start and end points and to need a minimum of explanation of the behaviour pattern to which they referred. To distinguish short, acute cries the symbol '√=crying for less than one minute' was printed above the time rulers. Considerable inconsistency was noted in the use of this symbol, however, as many parents disregarded it and so it was subsequently ignored. In addition, parents were asked to indicate the type of feeding (breast or bottle), the time of recognition of a bowel movement, periods not in contact with the infant, and any unusual occurrences during the day.

Diaries were available in English and French and to ensure that they meant the same in each language they were translated from English to French and then back from French to English, and then checked for ambiguity.

Showing the mother how to use the diary seldom took longer than five minutes. It was emphasised that all behaviour was to be coded by one of the available symbols. Mothers were questioned to be sure that they understood the temporal subdivisions of the time ruler. The only definition that was provided was for the category of 'fussing'. This had been added at the request of parents who wanted a symbol to cover behaviour that was 'not quite crying but not awake and content either'. All the other categories of behaviour were assumed to be self evident. Parents were told that diaries should be filled in when convenient and that they were not to disrupt their daily activities. They were not told how often to record.

RECORDING OF VOCALISATIONS MADE BY INFANTS

Rebelsky and Black used a voice activator circuit when recording vocalisations made by infants from fixed microphones attached to the cot[5-10] and other workers used telemetric techniques in adults,[11 12] adolescents,[13] and children.[14-17] In this study the tape recordings were made using a voice activated recording system that combined the advantages of radiotelemetry (freedom of movement) and a voice activator circuit. The system allowed continuous 24 hour recordings to be made with simultaneous recording of a time code on a second channel. It comprised a small microphone and radiotransmitter (weighing 42 g) fitted into a light cotton shirt so that the microphone could be placed about 7 cm from the infant's mouth. A thin wire aerial hung loosely at the side with the distal end tucked under the nappy. The transmitter was powered by two 1·5 volt batteries and was switched on continuously throughout a recording session. The vocalisations made by the infant, and other sounds picked up by the microphone, were relayed to a frequency modulated receiver, and then through a control panel to a UHER 4400 JC tape recorder. The control panel incorporated a voice activator circuit that automatically turned on the tape recorder and then turned it off after seven to 10 seconds of silence. On the second channel pulses from a time generator were registered at five second intervals whenever the recorder was on. The receiver was adjusted so that all vocalisations made by the infant were recorded, as were all other sounds that exceeded that threshold. The tape ran at a speed of 6 cm/second. A 24 hour continuous monitoring session usually produced from one to three hours of recording.

RECORDING PROTOCOL

The parents were not responsible for the functioning of the system, which was already connected and housed in a wooden box 62×32×23 cm placed centrally in a convenient location. The microphone and transmitter were put into the shirt by the research assistant. The parents were instructed to put the shirt beside the infant while the nappy was being changed. The sensitivity of the transmission was determined in response to the vocalisations the infant made, and its quality was checked from all relevant rooms. Once the system was in use, the diary was reviewed. The study was described as the collection of information on the behaviour patterns of normal infants. The parents were told that the tape recorder was an easy way to record the sounds made by the infant for 24 hours without disrupting the family's routine.

TRANSCRIPTION

Sounds on the tape were categorised as 'negative vocalisations', 'non-negative vocalisations', parents' vocalisations, and other sounds—for example, sheets rustling and the noise of the vacuum cleaner. A distinctive 'zeep' sound indicated that the tape had been activated so that the beginning and end of each recorded period could easily be distinguished. The time signal was shown on a digital clock, and at least one time marker was shown each time the tape was activated. By listening to the playback the presence, time, and duration of each sound could be indicated sequentially on a transcription sheet. All tapes were transcribed by a single observer, and only the infant's negative vocalisations were transcribed. Four randomly selected tapes were retranscribed and intraobserver reliability was determined separately for transcribing the frequency (events in 24 hours) and duration (seconds in 24 hours) of negative vocalisations (r>+0·99 for both, Pearson's product moment coefficient). Events lasting less than five seconds (usually one to two seconds) accounted for 47% of the frequency but only 7% of the total duration of negative vocalisations.

EDITING, REDUCTION, AND ANALYSIS OF DATA

It was apparent from studying the transcripts of the tape recordings that negative vocalisations tended to cluster together, being separated by long periods of silence, as might be expected from direct observation of crying and fussing in the infants. It was assumed that the crying or fussing symbols used in the diary represented these clusters, referred to as 'episodes.' Within these episodes, however, the actual vocalisations are not continuous, but are punctuated by inspirations and spontaneous pauses. Because the omission of the 'V' symbol from the diary and the absence of negative vocalisations of less than five seconds duration from the tape recording should not affect the reporting of the prolonged clusters of crying that were of primary interest, the diaries and tape recordings were first edited to eliminate these. The edited versions are the unreduced sets of data concerning the events of crying and fussing recorded in the diaries and negative vocalisations recorded on the tapes.

The data were then processed to obtain reduced sets of data. The smallest unit of recording in the diary is five minutes (the smallest subdivision on the time ruler) (fig 1). To identify clusters that the parents might have recorded as a crying episode, while eliminating short, isolated vocalisations, the following 'grouping and elimination' rules were applied to the unreduced sets of data (fig 2): two or more events separated from each other for five minutes or less were counted as one episode; the duration of crying for an episode was the arithmetic sum of the recorded negative vocalisations within the defined episode; after the application of the first

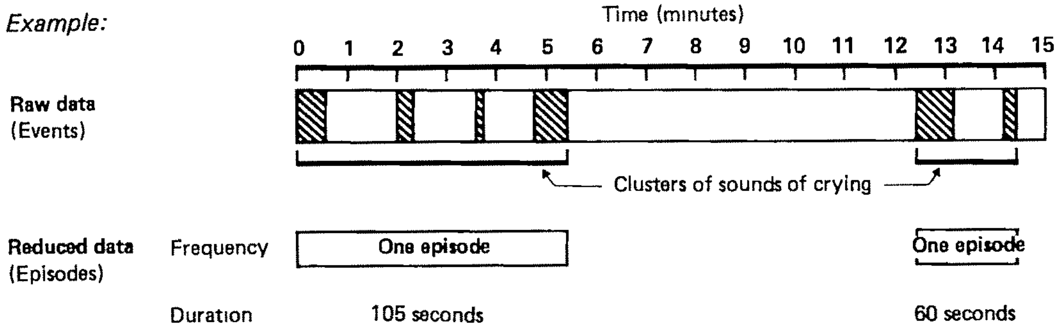


Fig 2 *Example of how frequency and duration of episodes of negative vocalisations were determined. Two or more events which are separated from each other by five minutes or less are regarded as one episode*

two rules any episode lasting 30 seconds or less was excluded; and episodes that occurred when the parent was out of the house were excluded. Thus with the first cluster of events shown in fig 2 the four negative vocalisation events that were recorded during the first five minutes and 20 seconds would count as one episode lasting 105 seconds.

The only rule applied to the unreduced data reported in the diaries was the first, concerning the grouping of two events separated by five minutes or less. Because there are two categories in the diaries (cry and fuss) which could be used to represent negative vocalisations, it was interesting to know whether the overall duration of negative vocalisation was more strongly correlated with crying, fussing, or crying and fussing combined. Consequently the category 'cry and fuss' was defined as a composite of all crying and fussing episodes. Its duration was the arithmetic sum of the duration of all episodes of both crying and fussing on the diary. The frequency of episodes was calculated from the arithmetic sum of all the episodes of crying and fussing on the diary, but adjacent episodes were classed as one.

The resulting transcripts and diaries constituted the reduced sets of data giving the duration (minutes in 24 hours) and frequency (episodes in 24 hours) of negative vocalisations from the tape recordings and crying, fussing, or both, from the diaries. From the second rule (that defined duration on tape recordings) it was apparent that the durations of the episodes of negative vocalisations that were recorded were much less than those recorded in the diaries. If parents associated negative vocalisations equally with crying and fussing symbols, the correlations of duration of episodes recorded on the tape with crying and fussing recorded in the diary should have been similar. On the other hand, if parents associated negative vocalisations more with crying than with fussing symbols in the diary, the correlation should have been stronger with cry than with fuss, or with the combination. The frequency only refers to clusters of negative vocalisations regardless of the duration of particular negative vocalisations within the cluster. Consequently, the only useful comparison for frequency is between the number of combined crying and fussing episodes recorded in the diary and the number of negative vocalisation episodes on the tape recording.

As indices of how diary recordings represent episodes of negative vocalisations, three comparisons were made. Firstly, Pearson product moment correlations between frequency and duration measures from diary and tape recording methods were calculated for the reduced sets of data. Secondly, as an index of the completeness of the parents' recording the reduced sets of data were compared to determine the total duration and frequency of episodes missed by the diary records.

To work out differences in individual interpretations of the symbols for 'cry' and 'fuss' the diary records of episodes of crying and fussing that corresponded in time with tape recorded episodes of negative vocalisations were used to derive measures separately for cry and fuss symbols of the average duration of negative vocalisation events, the number of negative vocalisation events each minute, the total duration of negative vocalisations each minute, and the cry:fuss ratio of the total duration of negative vocalisations each minute

USE OF THE DIARY IN A SAMPLE OF THE GENERAL POPULATION

A slightly modified version of the diary was used in a large prospective study to determine the causes of overweight in infants.[9 18] Normal subjects were recruited from the neonatal nursery of a large general hospital associated with the university.[9] Diaries and instructions for their use were given to the parents at home when the baby was 6 weeks old.

The diaries were kept for seven days and then returned in a stamped, addressed envelope. If they were not received within two weeks the parents were telephoned to remind them.

Results

COMPARISON OF TAPE RECORDINGS AND DIARIES

Satisfactory legible reports were obtained from all the parents. Most said that they had filled in the diary every two to four hours, usually during a routine activity such as feeding or nappy changing. Technically adequate tape recordings were obtained from all subjects.

Table 1 shows the duration and frequency of episodes of crying, fussing, or crying and fussing combined, from the diaries and negative vocalisations from the tape recordings. The combination of clusters of negative vocalisations into episodes on the tape recording with a mean frequency of 10·5 episodes in 24 hours was comparable with the number of combined crying and fussing episodes recorded in the diaries (mean 9·5 episodes in 24 hours). As expected the mean total duration of combined crying and fussing recorded in the diary (125 minutes in 24 hours) was much greater than the total duration of recorded negative vocalisation episodes on the tape (29 minutes in 24 hours). This was partly due to the more detailed recording of the intermittent sounds and pauses on the tape recording. In the diaries crying accounted for 53% of the frequency but only 43% of the duration of the total amount of crying and fussing.

Table 2 shows the correlations of the frequency and duration of crying and fussing episodes recorded in the diaries with the negative vocalisation episodes recorded on the tapes. The correlation between frequency of combined crying and fussing episodes and negative vocalisation episodes was moderately strong (r=+0·64, p=0·03) One diary was much less accurate than the other nine because three negative vocal sation episodes that had been recorded on th tape had been omitted from the diary, and thre other negative vocalisation episodes on the tape ha been amalgamated into one crying episode on th diary Both inaccuracies reduce considerably th frequency count for this diary and significantly affec the correlation for this small group. The strength o the association for frequency between recordin methods for the other nine subjects is stron (r=+0·85, p=0·002). The correlation betwee diaries and tape recordings for duration measure was best for crying alone and negative vocalisation (r=+0·67, p=0·02); this comparison provided strong correlation when the same nine diaries onl were considered (r=+0·90, p=0·001). There was n correlation of fussing alone with negative vocalisa tions, and this diminished the correlation for com bined crying and fussing with negative vocalisations

Table 2 *Correlation of frequency and duration of episod of crying and fussing reported in diaries with negative vocalisations on tape recording in 10 infants*

Episodes reported in diary	*Correlation with episodes of negati vocalisations recorded on tape recor*	
	r value	*p value*
Frequency		
Crying and fussing	+0 64 (+0·85)	0 03 (0 002
Duration·		
Crying alone	+0·67 (+0·90)	0·02 (0·001
Fussing alone	−0 01 (−0·26)	0 44 (0 26)
Crying and fussing	+0 45 (+0 41)	0 09 (0 14)

Figures in parentheses are calculated from nine diaries after oth had been omitted

TAPE RECORDED EPISODES NOT RECORDED IN THE DIARIES

The 10 diaries were compared individually with thei corresponding tape recorded episodes that had no been noted as either 'crying' or 'fussing' in th

Table 1 *Comparison between diary recording and tape recording of frequency and duration of episodes of crying and fussing in 10 infants*

	Episodes reported in diary			*Episodes recorded on tape recorder negative vocalisations*
	Crying	*Fussing*	*Crying and fussing*	
Frequency.				
Mean (SD) No of episodes in 24 hours	5 [illegible] (3 3)	5 1 (2 3)	9·5 (3 0)	10 5 (2 3)
Range	– 0	1–10	4–14	7–14
Duration				
Mean (SD) No of minutes in 24 hours	53 3 (33·9)	71 8 (44 9)	125·0 (48·1)	28 9 (14 6)
Range	10– 03	10–170	40–200	11 9–57·9

diaries tabulated. Parents missed an average of 20% of the total duration of negative vocalisation episodes and 14% of the total number of episodes. Missed episodes were not more common during the night.

DIFFERENCES IN THE USE OF SYMBOLS FOR CRYING AND FUSSING

To characterise the use of the symbols we only compared those episodes that were recorded both in the diary and on the tape. From the definition of fussing that had been given to the parents we expected that the parents would be more likely to use a cry symbol to describe clusters in which the average duration of the negative vocalisation events was longer and the number of negative vocalisations more frequent, while the fuss symbol would be used for clusters with shorter and less frequent vocalisations.

There were large differences among parents when using these symbols, and one parent did not use the fuss symbol at all. Table 3 shows that the number of negative vocalisation events in clusters designated 'cry' were more frequent (0·67 and 0·25 events a minute, respectively) but not longer (each event lasting 29 and 28 seconds, respectively) than those designated 'fuss'. Consequently each minute of 'crying' represented more total seconds of negative vocalising than 'fussing' (17·3 and 8·7 seconds for each minute, respectively). Individual subjects' cry:fuss ratios indicated that seven of the nine parents used 'cry' to designate more negative

Table 3 *Characteristics of negative vocalisations on tape recording referred to in diaries as 'cry' and 'fuss' in nine infants* values are expressed as median (range)*

	Cry	*Fuss*
Duration of negative vocalisation event (seconds)	29 (13–47)	28 (13–84)
Frequency of negative vocalisation events/minute of diary recording	0 67 (0 32–2·8)	0·25 (0 09–1·20)
Duration of negative vocalisation/minute of diary recording (seconds)	17·33 (4·2–60 0)	8·67 (2·43–48·25)
Cry.fuss ratio of total duration of negative vocalisation/minute of diary recording	2 5 (0 1–25·4)	

*One parent did not use the 'fuss' symbol and has been omitted

Table 4 *Characteristics of the mothers to whom diaries were sent, and their infants*

	Diary not returned (n=35)	*Diary incomplete or illegible (n=10)*	*Diary completed (n=374)*	*p value**
Maternal characteristics				
Mean age (years)	28	31	28	NS
Marital state (% single)	6	0	3	NS
Socioeconomic group[8]	61·6	58 8	64 4	0 04
Nationality (%)				0·04
Anglo-Canadian, United States, United Kingdom	26	20	48	
French Canadian, France	26	0	14	
Other European	8	10	9	
Mediterranean	14	30	11	
Other	26	40	18	
Type of feeding at birth (%)				0 02
Breast	46	40	62	
Formula	40	40	16	
Mixed	14	20	16	
Type of feeding at 6 weeks (%)				NS
Breast	25	20	36	
Formula	53	50	36	
Breast plus ≥one bottle	10	30	17	
Whole cows' milk	3	0	2	
Mixed	9	0	9	
Characteristics of infants				
Sex (% male)	54	50	55	NS
Mean birth order	1 8	2·4	1·6	0 01
Mean infant temperament questionnaire score[9 18]	16 0	14·3	16 7	NS

*Difference between complete diaries and those not completed or not returned (χ^2 or Student's unpaired *t* test).

vocalisation a minute than 'fuss' (1·6 to 25·4 times more) but the other two did not. Therefore, though there was a tendency for clusters of crying to represent a larger quantity of recorded negative vocalisation, the considerable variation between subjects suggested a wide range of individual recording styles.

USE OF THE DIARY IN A SAMPLE OF THE GENERAL POPULATION

Of the 409 eligible parents diaries were not received from 35 either because they did not complete them (n=10), or because they said they did but failed to return them (n=25), equalling a response rate of 92%. Of the 384 diaries recovered, 10 were incomplete or illegible, leaving 91% for analysis.

Table 4 shows the characteristics of the families in each group. Those who did not return them or who did not complete them correctly were similar. The mothers tended to be in a lower socioeconomic group and of Mediterranean or non-European origin, and they were more likely to choose formula feeding at birth. The infants tended not to be the first born. The only additional difference when comparing mothers whose diaries were returned but incomplete with those returned and complete was that they were older (31 and 28 years, respectively)

Discussion

Parents' records of infant behaviour patterns are useful in that they are inexpensive and large numbers of infants can be observed over long periods of time. For clinical and epidemiological purposes they are probably the only reasonable way of studying crying patterns, as these patterns vary from day to day and change significantly during the first three months of life,[1-3] and multiple recordings of many infants are needed to reduce the variability due to sampling error inherent in small numbers of observations. With a less variable measure of crying, clinicians may be able to determine what factors if any predispose to crying[18] and how specific interventions may affect them.[19] We typically record only duration and frequency of episodes but it is these that are of interest to clinicians, and diaries will only help if they can be shown to be a reasonably accurate measure of these.

Our results suggest that diaries provide useful short term recordings of the vocal component of crying. The duration of two and one-quarter hours of combined crying and fussing behaviour recorded by diary is similar to previous reports for infants of this age.[1-3] This represented only 30 minutes of negative vocalisations, but this is probably because parents also perceive infants as being distressed on the basis of motor behaviours when they are not crying and the tape recorded only the vocalisations. The moderate correlations with negative vocalisations for frequency of combined crying and fussing episodes and for duration of crying were satisfactory for the whole group. If the single poor diary is indeed atypical then the correlations between these measures may be stronger. These correlations were expected to be conservative estimates because of the isolation by audiotape of vocal aspects of crying, the differences in degree of detail between recording methods, dependence on recall, and the emphasis on simplicity and ease of use of the diaries. In studies limited to well motivated parents who would be required to make more frequent recordings in the diaries, better correlations might be obtained.

The strength of the associations was also affected by the reporting styles of individual parents. Our methods for grouping the data obtained from the tape recordings imposed a degree of consistency on the recordings, but were perhaps not sensitive enough to account for the widely varying styles. For example a 'ten minute rule' would have improved the frequency correlations but reduced the sensitivity of the measures to reflect differences between individuals. In this sense the use of the 'five minute rule' provides a more conservative estimate of the accuracy of the diaries.

There have been many reports of crying patterns[20] but fussing has received less attention.[21 22] We included it in this study at the request of parents who wanted a category between 'crying' and 'awake and content'. As it is less intense than crying it might have been expected to be associated with shorter and less frequent negative vocalisation events. While the total duration of negative vocalisation was less, this was because of a decreased number of (rather than shorter) vocal events. There was, however, a great deal of variability among subjects concerning both the frequency and duration of events included in a crying or fussing episode. The fuss symbol was probably used by some parents to indicate agitated motor behaviour not accompanied by much sound. Differences in recording styles, the shorter duration of vocalisation associated with 'fussing' and the use of the fuss symbol to refer to primarily motor behaviour may explain the absence of a correlation between diary recording of 'fussing' and tape recording of negative vocalisations. This does not imply that the 'fuss' symbol was used less accurately but that the behaviour was different. On the contrary, diaries may well be more accurate than tape recordings for studying patterns of distress, since tape recordings capture only the vocal components of distress behaviour.

The usefulness of the diaries depends not only on what and how accurately they record, but on how acceptable they are to parents Our results suggest that though we obtained appropriate data which we could interpret from 90% of the subjects this may have represented a biased sample in that families of lower socioeconomic groups, ethnic minorities, large families, older mothers, and children who were formula fed from birth may be under represented.

Our findings have several implications. First, the extent of agreement between diary recording and tape recording may have been favourably biased by the presence of the recorder, the novelty of the procedure, and the short duration of the recording period. On the other hand, the lack of interference (filling in the diary when convenient), the simplicity of instructions, and the lack of a formal practice session may have resulted in less than optimal recordings. In particular applications more accurate recordings could probably be achieved—for example, in small studies with well motivated parents.

Secondly, the differences in the use of the 'cry' and 'fuss' symbols indicate that (contrary to common practice) the two concepts should not be considered synonymous. Some papers about crying and colic use the terms interchangeably.[1] [2] They are often used to indicate degrees of severity of distress,[21] [22] but some use fussing to indicate 'unexplained' crying.[6] Our results show that the symbols were not used interchangeably by parents and that other behavioural features may have played a part in the designation of fuss. As a result diaries with a symbol for cry only may not be recording an important sign of infant distress, whereas diaries that refer to fussing only may not capture a marker of severity of distress distinguishable by the parents.[21]

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Infant feeding and allergy

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SUMMARY The effect of withholding cows' milk was examined in 487 infants at high risk of allergic disease. Before birth they were randomly allocated either to a control group, most of whom received cows' milk preparations, or to an intervention group, who were offered a soya based substitute. Eczema and wheezing occurred to a similar extent in the two groups during the first year of life, although napkin rash, diarrhoea, and oral thrush were commoner in the intervention group, especially during the first three months. Breast feeding for any length of time was associated with a reduced incidence of wheezing and diarrhoea.

In 1936 it was first suggested that bottle fed infants are more liable to eczema than those who are breast fed.[1] During the past 50 years numerous studies have been published on the relation between infant feeding and allergy. In several (but not all) of these studies the findings have suggested that the mode of feeding during the first few months of life affects the risk of allergic disease in subsequent years.[2] It has not been clear as to whether the association—if it is causal—arises from a protective effect of breast feeding or from an adverse effect of cows' milk and perhaps other foodstuffs. In some studies allergic disease occurred less often in children who had been given a soya preparation than in those given cows' milk. At the time the present study was set up only three randomised controlled trials investigating this subject had been published; one was very small,[3] one was invalidated by non-compliance,[4] and the third was apparently open to bias in that clinical assessment of the children was not 'blind'.[5] A randomised controlled trial was therefore set up in infants at high risk of allergic disease to determine whether withholding cows' milk reduced their risk of allergic disease. The hypothesis that breast feeding confers positive protection could not be tested by means of a controlled trial as it did not seem reasonable to allocate mothers to breast and bottle feeding randomly. The study did, however, provide observational data on the relation between allergic disease and breast feeding, other foods, and certain environmental factors. This paper presents the findings during these infants' first year of life.

Subjects and methods

Pregnant women were recruited at two antenatal clinics in South Wales. At the booking clinic all women were asked whether they, their husbands, or any of their children had ever suffered from eczema, hay fever, or asthma. Those who answered affirmatively were told about the study and asked if they were willing to participate. The women who agreed to take part were randomly allocated to an intervention or a control group by means of sealed envelopes containing cards that were coded according to a computer generated randomisation procedure. Those in the intervention group were asked not to give their babies cows' milk, or any food made from it, for at least four months. A soya preparation was supplied for those mothers not wishing to breast feed and for those breast feeding who wished to supplement their feeds. Mothers in the intervention group were advised to restrict their daily milk intake to a half pint (284 ml) during the pregnancy and while they were breast feeding.

A list of foods containing cows' milk (and therefore to be avoided for the baby) was given to mothers in the intervention group. Both groups of babies were followed up at home at regular intervals by a dietician, who supplied soya milk to the intervention group as required for six months. All the mothers were given diaries in which they were asked to record the type of milk they gave their babies and also the first time any new food was given.

The babies were examined at the ages of 3, 6, and 12 months by a physician (FGM) who was unaware of their allocation in the trial. The skin was examined for the presence of a rash; a diagnosis of eczema was made always by the same physician. The presence of any nasal discharge was noted, and the mothers asked whether the babies had had any thrush, napkin rash, diarrhoea, or wheezing (defined as a whistling noise coming from the chest) since the previous examination. Skin tests (using Bencard extracts) were performed at 6 and 12 months against certain common allergens; the foods tested were milk, cod, whole egg, wheat flour, and soya Blood was taken at birth and at 3 and 12 months for immunological assay, the results of which will be published separately.

The significance of differences in symptomatology between the study groups was assessed by means of a 2×2 χ^2 test statistic, using Yates's correction, the sample sizes being adequate in all cases for the application of this test.

Results

The numbers of babies available for the trial and those actually admitted to it are shown in table 1 The nine babies omitted because of non-cooperation were never effectively admitted to the trial as their mothers changed their minds about participating at or soon after their birth; six of these mothers had been allocated to the intervention group and three to the control group. Ten babies were omitted because it was uncertain, owing to clerical error, whether they were allocated to the intervention or the control group. These infants were followed up in the same way as the rest, and the data used for observational purposes only. A further eight were excluded because they were born, or were about to move, outside the study area. The 487 infants admitted to the trial were all seen by the assessing physician on at least one occasion, except for one baby who died before the age of 3 months. Most infants were seen at 3, 6, and 12 months, but a few failed to attend for one or two assessments. The information about various symptoms was collected both from the mother's history and from the doctor's examination; occasionally one or other of these sources was incomplete, producing slight variations in the total numbers available for information about different symptoms. Feeding diaries were completed for the babies, dietary information being supplemented by notes made by the dietician as to the type of milk that had been given when the babies were 3 months old. Information on the second three months was slightly less complete than for the first three months in that some mothers ceased to maintain these diaries. The numbers of infants for whom the various items of information were available are shown in tables 2–5.

Table 2 compares the intervention and the control groups in various respects. The two groups were broadly comparable with regard to the mothers' age and parity, the families' social class and smoking habits, and the babies' sex and birth weight. The mothers in the intervention group were less likely to breast feed their babies than were those in the control group, possibly because they were offered a free supply of soya milk.

Table 3 shows the time at which cows' milk protein was first given to the babies in the two groups. The time of introduction refers to cows' milk in any form, whether as a powder or liquid preparation for bottle feeding or as an ingredient of some other food. Nearly all the control group received cows' milk protein within the first few weeks of life, whereas it was given to only about a tenth of the intervention group in the first month and to about a quarter in the first three months.

It was recognised that the withholding of foods containing cows' milk would tend to prevent other foodstuffs from being given to babies where those foodstuffs are combined with milk protein in prepared foods. Table 3 therefore shows the timing of introduction of egg and wheat or rye protein in the two groups. Seven babies are omitted from this part of the table as their mothers did not complete any

Table 1 *Infants admitted and excluded*

No of women recruited		527
No of twin births		6
No of total possible infants		533
Exclusions (% of possible subjects)		
Abortion, stillbirth	14 (3)	
Birth weight <2000 g	5 (1)	
Non-cooperation	9 (2)	
Uncertainty regarding randomisation	10 (2)	
Outside area	8 (2)	
Total No excluded (%)		46 (9)
No (%) of infants admitted to trial		487 (91)

Table 2 *Certain characteristics of intervention and control groups*

	Intervention group (n=238)	*Control group (n=249)*
Mean maternal age (years) (last birthday)	25·2	24·7
No (%) with smoker in house	118 (51)	129 (54)
No (%) from non-manual social class	66 (28)	53 (22)
No (%) from manual social class	131 (56)	139 (57)
No (%) of students/unemployed	37 (16)	51 (21)
No (%) of firstborn	91 (38)	104 (42)
No (%) of boys	119 (50)	137 (55)
Mean birth weight (g)	3320	3350
No (%) ever breast fed	78 (33)	107 (43)

Table 3 *Time of introduction of cows' milk, egg, wheat and rye proteins*

Food	*Group*	*No infants*	*Cumulative percentage of infants having received food*				
			Week 1–4	*Week 5–13*	*Week 14–19*	*Week 20–26*	*Week 26+*
Cows' milk	Intervention	238	11	26	44	61	100
	Control	249	91	96	98	99	100
Egg	Intervention	236	0	9	33	61	100
	Control	244	0	26	65	84	100
Wheat rye	Intervention	236	1	56	85	95	100
	Control	244	8	64	90	97	100

dietary diary; information about cows' milk and breast feeding was available from the dietician's notes in these cases. There is some uncertainty about the numbers who had not received the food by 6 months; where a food had not been shown in the diary by this time it was assumed that it had not been given, although in some cases the mother may have simply forgotten to record it. There is, however, no reason to suppose that the two groups behaved differently in this regard. Both egg and wheat protein tended to be given later in the intervention than in the control group, the difference being particularly great in the case of egg.

Table 4 shows the incidence of certain conditions during the first year of life in the two randomised groups. The total numbers vary slightly because of incomplete information in some cases. The incidence of eczema was higher in the intervention group than in the controls, but the difference was not significant, nor were the differences for wheeze or nasal discharge. There was, however, a significantly higher incidence of oral thrush in the intervention group No differences between the two groups emerged in regard to severity of eczema, nor as to whether it had been treated by a doctor.

With regard specifically to the first three months, napkin rash occurred in 132 out of 235 (56%) of the intervention group, and in 113 out of 246 (46%) of the controls ($p<0.05$). During this period, diarrhoea was reported in 83 (35%) of the intervention group and in 60 (24%) of the controls ($p<0.05$), although taken over the full year the difference was not significant. Within the first three months, diarrhoea and napkin rash were significantly associated with each other ($p<0.05$), and so were napkin rash and thrush ($p<0.001$), although the association between diarrhoea and thrush just failed to reach significance at the 5% level.

Table 5 shows the incidence of certain conditions during the first year of life according to whether the infants were breast fed and for how long, irrespective of their randomised allocation in the trial. The numbers of infants in this table are greater than those in table 4 owing to the inclusion of some who were excluded from the trial because their randomised allocation was uncertain. Wheeze occurred about twice as frequently in those never breast fed (125/293) as in those ever breast fed (41/189), the difference being highly significant ($p<0.001$). The breast fed infants had less diarrhoea (111/189) than the non-breast fed infants (224/293) ($p<0.001$); nasal discharge was also less frequent in those breast fed than in those never breast fed (72/186 and 132/282, respectively), but the difference was not significant. Duration of breast feeding was examined in relation to these symptoms by means of the Wilcoxon rank sum test in the breast fed infants; duration was significantly and negatively related to risk of diarrhoea ($p<0.05$) but not to risk of wheeze or nasal discharge. The incidence of eczema was similar in those ever and never breast fed (35% and 40%, respectively), so the effect of duration on eczema was not examined. Although 8% of the babies were breast fed for six months, exclusive breast feeding was rare, only eight babies (2%) receiving no other food in their first eight weeks of life. The effects of exclusive breast feeding were therefore not examined.

In view of the greater tendency of the control

Table 4 *Incidence of certain conditions during first year according to allocation in trial*

Condition	*Intervention group*		*Control group*		*Significance level*
	Total No	*No (%) affected*	*Total No*	*No (%) affected*	
Eczema	223	94 (41)	233	80 (34)	NS
Wheeze	232	84 (36)	242	80 (33)	NS
Nasal discharge	223	96 (42)	232	104 (45)	NS
Thrush	232	118 (51)	242	97 (40)	$p<0.05$
Diarrhoea	232	167 (72)	242	161 (67)	NS

Table 5 *Duration of breast feeding and incidence of wheeze, nasal discharge and diarrhoea in first year of life*

Symptom	*Duration of breast feeding (weeks)*				*Any breast feeding*	*All infants*
	0	*<1–4*	*5–25*	*26+*		
Wheeze						
Total No	293	85	64	40	189	482
No (%) affected	125 (43)	20 (24)	10 (16)	11 (28)	41 (22)	166 (34)
Nasal discharge						
Total No	282	85	63	38	186	468
No (%) affected	132 (47)	38 (45)	21 (33)	13 (34)	72 (39)	204 (44)
Diarrhoea						
Total No	293	85	64	40	189	482
No (%) affected	224 (76)	54 (64)	42 (66)	15 (38)	111 (59)	335 (70)

group to breast feed in comparison with the intervention group, the incidence of eczema, wheeze, nasal discharge, and diarrhoea in the two randomised groups was compared after adjusting for breast feeding.[6] No differences approaching significance were found for any of these conditions. When social class and the presence of smokers in the house were taken into account, breast feeding was still negatively associated with wheezing and diarrhoea. Details of these and of other related factors will be published separately.

The feeding diaries were examined to see whether various foods had been introduced at an earlier age for infants who developed eczema compared with those who did not. No difference was found in the ages at which milk, wheat and rye, egg, beef, other meat, or fruit had been introduced. For the whole cohort of infants, the median week at which each foodstuff was introduced was as follows: cows' milk protein, week 2; wheat or rye, week 12, egg protein, week 20; beef, week 16; other meat, week 16; fruit (usually as juice), week 7; most had not received fish by 26 weeks. Infants who wheezed tended to have received wheat or rye protein significantly earlier, and beef significantly later, than infants without a history of wheezing ($p<0{\cdot}05$ using the Wilcoxon rank sum test in each case).

The results of the skin tests at one year were examined according to whether the infants did or did not acquire eczema at some time during their first year of life. The only food antigen which was associated with eczema was egg, for which a positive skin test (weal of 3 mm diameter or more) was obtained in 26 out of 177 babies with a history of eczema (15%), compared with seven out of 288 without eczema (2%) ($p<0{\cdot}001$). No other foodstuff produced a positive reaction in more than three infants in either the eczematous or the non-eczematous group.

Discussion

The possibility that infant feeding affects the risk of subsequent allergy can be expressed as three alternative hypotheses. Firstly, cows' milk (and perhaps certain other foods) in early life may be specifically allergenic; secondly, any food other than breast milk may promote allergic disease; and thirdly, breast milk may be specifically protective. The present study tests the first hypothesis by means of a randomised controlled trial, and provides observational evidence on the third hypothesis; it cannot address the second hypothesis because of the rarity of exclusive breast feeding in this population. A recent attempt was made to test the second hypothesis in a controlled trial, but without success in that exclusive breast feeding occurred to the same extent in the intervention and control groups.[7] There was, however, less eczema in breast fed infants, supporting the third hypothesis. An earlier controlled trial tested the first hypothesis[5]: cows' milk was replaced by soya milk, and egg, wheat, and beef were excluded until the children were 7 months old. Ten years later the intervention group had significantly less asthma and allergic rhinitis than the controls, although the lack of blind assessment leaves open the possibility of bias.

Numerous observational and non-random part intervention studies have been published on the subject. In four recent studies breast feeding, or the avoidance of cows' milk and early solids, was associated with a lower incidence of allergy, especially in high risk infants.[8–11] Others have shown little or no relation, however,[12 13] while one paper reported a positive association between breast feeding and eczema.[14] Earlier studies showed a similar lack of agreement.[2] It is difficult to assess the strength of this evidence as it was seldom clear whether detailed information was collected continuously in a manner which would have shown an occasional milk supplement. Still fewer studies seem to have incorporated blind assessment into the study design, so that some bias may (however unintentionally) have intruded. The present study was designed to avoid these weaknesses as far as was practicable. The feeding diaries provided dietary information from day to day, and compliance appeared to be reasonably good. Admittedly some babies in the intervention group were given cows' milk protein, a quarter of them having received it on at least one occasion by the age of 13 weeks. But the difference between the two groups in this regard (96% receiving cows' milk in the control group compared with 26% in the intervention group) was such that an important protective effect of cows' milk avoidance seems very unlikely, particularly in view of the fact that eczema and wheezing occurred more frequently in the intervention group. Some mothers may of course have forgotten to record certain foods, but most of them seemed to take the study seriously. Although the mothers in the intervention group were advised to restrict their own milk intake, the study was not designed to test the effect of maternal antigen avoidance, which may be important in the prevention[15] and treatment[16] of infantile eczema.

The diagnosis of eczema is inevitably subjective, and it is possible that another physician might have diagnosed some of the rashes differently. But the infants were all seen by the same physician, whose criteria of diagnosis were at least consistent. Furthermore, it is remarkable that the one year incidence of eczema (38%) was precisely the same as that reported in the recent study of very similar design conducted in Bristol.[7] The clinical assessment was indeed blind and the physician remained unaware of the infants' allocation within the trial and of their actual feeding history, so that diagnostic bias was excluded.

It was not possible to conduct the trial in a double blind manner, nor to control everything that the mothers gave their babies. Inevitably they knew which group they were in, and their behaviour may have been influenced in unforeseen ways by the offer and delivery of free formula. One such effect was the lower incidence of breast feeding in the intervention group. When this tendency was allowed for there was still no difference between the two randomisation groups in respect of eczema, wheezing, or nasal discharge. But the possibility must be recognised that other unsuspected biases may have operated.

The findings so far give no support to the belief that withholding cows' milk reduces the risk of allergic disease. It is of course possible that cows' milk and soya milk are equally allergenic. Soya allergy is known to occur,[17 18] and it may be that if some other milk substitute had been used the incidence of allergy would have been reduced. In view of the evidence from some of the earlier studies, it seemed reasonable to assume that soya milk was likely to be less allergenic than cows' milk. But perhaps the allergenicity of cows' milk formulae has been sufficiently reduced in the last 30 years for all advantage of soya to disappear. These results relate only to the first year of life; the infants are being followed up to see whether an effect appears in the future, as might be expected from the trial of Johnstone and Dutton.[5] The soya milk did appear to cause more diarrhoea, napkin rash, and thrush, and while these conditions were not usually serious they have to be considered as disadvantages to be weighed against any potential (and uncertain) reduction in allergic disease. The associations between these three symptoms suggest that the effects of soya milk upon them may be interrelated, apart from the fact that diarrhoea aggravates napkin rash, the mechanisms of these effects can only be conjectured.

A randomised controlled trial provides more reliable evidence on aetiology than does an observational study. Some caution is therefore called for in interpreting the observed assocations in this study that were not part of the randomisation design. Mothers who choose to breast feed or delay the introduction of various foods to their infants' diets may differ from other mothers in various ways relevant to the risk of allergic disease. With this proviso the infants can be regarded as constituting a cohort in which the determinants of allergy can be studied prospectively.

Breast feeding was clearly associated with a halving of the incidence of wheeze, and a significant reduction in diarrhoea. The possible immunological basis of these effects will be discussed in a further communication, but obviously the mechanism may not just involve allergic disease. There is some evidence that breast feeding reduces the risk of respiratory syncytial virus infection.[19] The duration of breast feeding did not seem so important in relation to wheezing as whether or not the infants had been breast fed at all. Relatively few babies were breast fed for six months, and even fewer were exclusively breast fed for as long as eight weeks, other foodstuffs (particularly fruit juice) being introduced early in most cases. It therefore seems likely that even small quantities of breast milk have a positively protective effect irrespective of other foods being given. If the skin tests are taken to represent allergy to foods, egg may well be involved in infantile eczema, as other workers have suggested,[20] although the age at which it was introduced seemed to be unimportant. The observation that wheezy children tended to have received wheat or rye protein earlier than others may be relevant; wheat protein has been suspected as potentially allergenic, and it is antigenically very similar to grass pollen, a major culprit in allergic disease. The fact that beef was introduced later on average to the diet of wheezy infants was presumably fortuitous, as it is difficult to see how beef could be protective.

It seems reasonable to conclude that breast feeding appears to be highly advantageous, and that no evidence has so far emerged to suggest that soya milk is better than cows' milk in regard to the risk of allergic disease. We shall continue to follow up these babies to see whether there is any evidence of long term benefit of early avoidance of cows' milk.

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Neonatal patient triggered ventilation

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SUMMARY Patient triggered ventilation was assessed in 14 neonates (gestational age 24–40 weeks). Inspiratory changes in airflow, monitored by a pneumotachograph, were used to trigger the ventilator and this was not associated with complications. Patient triggered ventilation was maintained for up to eight hours (mean duration five hours). In 13 of 14 infants oxygenation improved and this was associated in most with an increase in rate of delivered positive pressure inflations and inflating volumes. A greater improvement in oxygenation was shown when trigger mode was used during the recovery phase of respiratory distress syndrome. Only one infant, who made very little respiratory effort, failed to improve. We conclude that patient triggered ventilation may be used as an effective form of neonatal ventilation.

In a previous study we showed that patient triggered ventilation was feasible even in very preterm infants.[1] We used oesophageal pressure changes to detect respiratory efforts and these pressure changes were then used to trigger the ventilator. In all infants this form of ventilation was associated with improvements in both inflating volume and oxygenation, as evidenced by transcutaneous monitoring. There was minimal interference from peristalsis. The major disadvantage, however, with using oesophageal pressure changes or abdominal movements (as has been done previously[2]) to detect respiratory efforts is the inability to differentiate correctly between obstructed and non-obstructed breaths.[3] During an obstructed breath, which occurs as a result of a blocked endotracheal tube, respiratory efforts may continue and would be sensed either by changes in oesophageal pressure or abdominal movements despite the absence of airflow. Thus obstructed respiratory efforts can only be reliably detected as the absence of gas flow at the airway. The safest and most reliable trigger site, therefore, is likely to be flow changes at the airway. The present study investigated the practicality of using airflow changes as the patient trigger to a suitably modified ventilator

Patients and methods

Fourteen infants were studied on 20 separate occasions, all were less than a week old and had a mean gestational age of 29 weeks (range 24–40 weeks). The infants had a variety of diagnoses: 11 had respiratory distress syndrome, one birth asphyxia, and two respiratory distress associated with severe prematurity—that is <26 weeks' gestation. These infants represented 14 consecutive babies ventilated on the neonatal intensive care unit. Infants were studied during the first neonatal week according to the availability of the trigger ventilator, thus they were at varying stages in their respiratory illness. Three of the 14 babies, all suffering from respiratory distress syndrome, were studied on three separate occasions during their respiratory illness.

Ventilatory support was by an SLE Newborn 250 ventilator. Ventilator settings were determined before the study by the clinical team caring for the infant: rates varied from 10–60/minute, peak inspiratory pressures 15–26 cm H_2O, inspiratory times were restricted to 0·5 seconds.[4] No infant was paralysed or sedated, but those on ventilator rates less than 30/minute were receiving treatment with a methylxanthine.

Infants were entered into the study once stable on conventional ventilation for at least 2 hours. They were then switched to continuous positive airways pressure (CPAP) trigger mode. Patient triggered ventilation was delivered by a modified SLE 250 Newborn ventilator. The ventilator has a manual breath control which in CPAP mode allows delivery of a single positive pressure inflation, of magnitude and duration conforming to that predetermined during intermittent positive pressure ventilation mode. An interface has been developed such that only if a critical change in inspiratory airflow (>0·4 l/minute) is exceeded will the manual breath control be triggered (systems delay up to 40 milliseconds can be experienced). The ventilator has also been modified so that after roughly eight seconds, if the sensor has failed to detect respiratory efforts of sufficient magnitude to trigger the ventilator, then a manual breath is delivered.

Airflow changes were monitored using a pneumotachograph (Mercury F10L) placed between the endotracheal tube and ventilator circuit. This device recorded flow, inspiratory flow changes triggered the ventilator. The pneumotachograph was attached to a Validyne pressure transducer (range±2 cm H_2O), the signal of which was electronically integrated by a Gould Integrator (model no 13–4615–70) The pneumotachograph was calibrated at the beginning and end of each study period, on no occasion did the characteristics of the pneumotachograph change. Oesophageal pressure changes were monitored using an oesophageal balloon and catheter system[5] attached to the Validyne pressure transducer (range±50 cm H_2O). Ventilator pressure changes were monitored from the infant's side of the pneumotachograph (Validyne pressure transducer range±50 cm H_2O)

Flow, volume, oesophageal and ventilator pressure changes were recorded simultaneously on a Polygraph (Gould model no 2800S). Recordings were made 20 minutes before starting trigger mode and during the initial 20 minutes on trigger mode. Arterial blood gases were checked from an indwelling arterial catheter 20 minutes before changing to trigger mode—that is, immediately before the connection of the pneumotachograph in the circuit—then 20 and 60 minutes later and subsequently as clinically indicated (at least every four hours) throughout the period of trigger ventilation. An arterial blood gas was again checked 20 minutes after discontinuing trigger mode Throughout the period of ventilation the infants were continuously monitored either using a Searle intra-arterial electrode or a transcutaneous oxygen monitor (Draeger). If the transcutaneous monitoring showed oxygenation to be decreasing (>1·33 kPa) an arterial blood gas was immediately checked, and if this confirmed the change, the infant was immediately returned to conventional ventilation Otherwise trigger ventilation was maintained while one of the researchers (AG) was within the neonatal intensive care unit: the recording equipment rather than the ventilator required supervision.

The magnitude and rate of the infant's spontaneous respiratory efforts were assessed from the oesophageal pressure recording. By comparison of the oesophageal and ventilator pressure record it was possible to determine the infant's interaction to positive pressure inflation.[6,7] Ventilator rate and inflating volume were calculated from the whole of the 20 minute recording before starting trigger mode and the initial 20 minutes on trigger mode and then expressed as the mean for each 20 minute period. To assess the effectiveness of trigger mode ventilation, ventilator rate, inflating volume, and arterial blood gases during the different modes of ventilation were compared.

Statistical analysis to assess if differences in the results using the two modes of ventilation were significant was performed by a paired Student's *t* test.

Ethical permission for the study was granted by the hospital ethics committee.

Results

In most of the infants the delivered number of positive pressure inflations increased during the period of trigger ventilation ($p<0·05$, see table) compared with conventional ventilation. The rate only decreased in one infant in whom trigger ventilation had to be discontinued after 20 minutes due to a deterioration in oxygenation (from 8·65 kPa to 5·47 kPa). The infant (24 weeks gestational age) had previously suffered bilateral grade IV intraventricular haemorrhages and had made very little spontaneous respiratory effort. Delivery of positive pressure inflation decreased from 20 to 8–12 breaths/minute during trigger mode (8 breaths/minute was the maximum rate delivered by the ventilator in apnoea mode).

Delivered volume remained constant or increased during trigger mode ($p<0·02$, see table). Respiratory efforts during trigger mode were synchronous. Improved volume exchange on trigger mode was seen among the infants who were actively expiring during conventional ventilation.

In 13 infants, during the first hour of trigger ventilation, oxygenation improved falling only in the infant who was apnoeic. Comparison of the results

Table *Comparison of the two modes of ventilation. Results are mean (range)*

	Conventional ventilation	*Trigger mode after one hour*
Volume (ml)	6 0 (2 5–20)	6 8 (4–20)
Ventilator rate (breaths/minute)	46 (5–70)	55 (12–74)
pH	7 28 (7·2–7·4)	7 29 (7·2–7 45)
PaO_2 (kPa)	9 06 (6 67–12·7)	10 3 (8·93–13·9)
$PaCO_2$ (kPa)	5 47 (4 27–6 67)	5 73 (3 33–6 40)

after one hour on trigger mode with those on conventional ventilation showed a significant improvement in PaO_2 ($p<0·02$, see table). During a similar period there was no significant change in pH or PCO_2. In one (25 weeks gestational age) of the 13 infants in whom oxygenation had improved and was maintained, a respiratory acidosis developed at two hours, and this was associated with a reduction in the number of triggered breaths suggesting a decrease in respiratory efforts. Among the other 12 infants the period of trigger ventilation continued for between three and eight hours (mean five hours). None of these infants developed a respiratory acidosis and oxygenation was maintained. Trigger ventilation was discontinued for other intensive care procedures to take place, due to the inconvenience imposed by the size of the recording equipment.

Three infants were studied on three separate occasions during their respiratory illness within the first week of life. On all three occasions trigger mode ventilation was associated with an improvement in oxygenation, but this was greater during the recovery phase of respiratory distresss syndrome—that is, when the infants had been on conventional ventilation at ventilator rates less than 30 breaths/minute. In total, excluding the infant on trigger mode for only 20 minutes, on eight occasions infants were studied who had previously received rates less than 30 breaths/minute, and on 11 occasions infants were studied who had been on rates in excess of 55 breaths/minute. Comparison of the change in oxygenation after one hour on trigger mode between these two groups showed that the infants receiving a slower rate of conventional ventilation had a significantly greater change in oxygenation (mean 2·67 kPa, range 2·13–3·07 kPa) than those previously ventilated in excess of 55 breaths/minute (0·93 kPa, range 0·67–1·47 kPa), $p<0·02$.

Discussion

One of the aims of our investigation was to study this form of ventilation in a consecutive series of infants to assess its usefulness as a general mode of ventilation. Although most of our patients suffered from respiratory distress syndrome other diagnoses were included and we found patient triggered ventilation to be useful in most (13 of 14)—that is, oxygenation improved.

The results confirmed our previous findings that even very preterm infants show spontaneous respiratory activity during artificial ventilation and thus are capable of triggering the ventilator.[8] Our findings do, however, suggest that patient triggered ventilation may have only limited success in very preterm infants previously receiving 'full' conventional ventilation, as evidenced by the results of the two most immature infants (24 and 25 weeks gestational age) included in our study In one, suffering from bilateral grade IV intraventricular haemorrhages, oxygenation fell due to a lack of respiratory efforts and the second, after two hours, developed a respiratory acidosis.

The SLE ventilator in trigger mode incorporates an apnoea alarm, this ensures delivery of inflating pressures after roughly eight seconds. If an infant is apnoeic or with minimal respiratory efforts positive pressure inflation will only be delivered at a rate of 7–8 breaths/minute. This was insufficient to maintain oxygenation in the apnoeic infant included in our study. A more effective method of compensating for apnoeic periods would be for a minimum number of ventilator breaths/minute to be predetermined and if these were not triggered, they would be delivered automatically.

In all infants triggered ventilator breaths were only delivered at the beginning of inspiration ensuring synchronous respiration with ventilation, which is advantageous.[9] Detection of respiratory efforts by airflow changes also ensured that all apnoeas and episodes of blocked endotracheal tubes were correctly detected There are, however, two theoretical problems that could be encountered when using a pneumotachograph sited in the airway as trigger site. Firstly, the pneumotachograph used is unheated and during prolonged use could be affected by condensation, but it is used inside the heated incubator. The characteristics of the pneumotachograph were studied at the beginning and end of any study periods, and they remained unaltered. This lack of change in the resistance of the pneumotachograph suggested condensation had not been a problem. Secondly, the pneumotachograph, by increasing dead space, may lead to increased respiratory efforts and respiratory acidosis In this study, however, although infants were ventilated up to a maximum of eight hours, only one infant developed a respiratory acidosis. It should be noted, however, that although oxygenation improved after insertion of the pneumotachograph, carbon dioxide concentrations did not decrease during the first period of trigger ventilation despite the increase in minute volume. Subsequent arterial blood gases, despite maintenance of the pneumotachograph in the circuit, however, did not show increasing carbon dioxide concentrations; this suggested that the infant had accommodated to the increase in dead space, and in the absence of a respiratory acidosis, without important complications. Unfortunately, no infant was studied for longer than eight hours, as the recording equipment to which the pneumotachograph was attached could not be left unsupervised

It is obviously now important to test the long term effectiveness and possible side effects of this form of patient triggered ventilation using a pneumotachograph in the airway. As a consequence the patient triggered system has now been modified to consist only of a pneumotachograph and transducer directly attached to the ventilator and the effect of long term patient triggered ventilation is now being studied.

Infants were included in this study at varying stages of their illness, both during the acute and recovery phase. As the length of ventilation was restricted in each individual baby, however, it is not possible to comment on the suitability of this form of ventilation throughout the respiratory illness. Our results do suggest that it is more effective during the recovery phase. The greater improvement in oxygenation at this time is possibly due to the increased number of delivered positive pressure inflations, as had been seen previously [1] This increase may reflect an increase in respiratory efforts due to the use of methylxanthines during the recovery phase, which facilitated triggering.[10] This means that using the present system weaning during trigger mode can only be achieved by reducing pressure rather than rate of delivery of positive pressure inflations.

Although all infants with respiratory efforts were converted to synchronous respiration and none developed an air leak during trigger mode, as no long term studies were performed we cannot comment whether this form of ventilation would reduce the need for paralysis or alter the incidence of pneumothoraces.

We conclude that patient triggered ventilation is safe and effective in the short term among infants who show respiratory efforts, and it may be advantageous as it is associated with improvements in oxygenation. The practicality and effectiveness of patient triggered ventilation using airflow changes throughout the course of a variety of neonatal respiratory illnesses is now being investigated

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Urinary creatinine excretion in the newborn

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SUMMARY We measured the excretion rate of endogenous creatinine in 84 24-hour urine collections obtained from 60 term and preterm newborn infants between the 3rd and the 68th postnatal day, at postconceptional ages 28–42 weeks. The rate was positively correlated with weight, height, and postconceptional age but not with postnatal age; the strongest correlation was that with weight. When the rate was factored by weight it was constant across the range of values studied, with a median and logarithmic mean value of 90 μmol/kg/day (10 mg/kg/day) and a range (2 log SD) of 45–180 μmol/kg/day (5–20 mg/kg/day).

In 1913, Myers and Fine showed that the urinary excretion rate of creatinine was directly proportional to total body creatine content.[1] Shortly afterward Bürger reasoned that, as virtually all the creatine in the body is located in muscle, and as the creatine concentration in muscle is constant, the urinary excretion rate of creatinine must be proportional to muscle mass.[2] Measurement of the urinary excretion rate of creatinine has been used extensively in recent years in the assessment of nutritional state,[3 4] and it has been used as a yardstick against which to measure the normal excretion rates of other metabolites: the ratio of the urinary concentration of any substance x to that of creatinine (U_x:U_{cr}) provides a measure of the excretion rate of x which avoids the need for a timed urine collection, provided that the excretion rate of creatinine is known. Normal ranges for the urinary excretion rate of creatinine are available for infants and children after the neonatal period, as well as for adults,[5] but there is only one published study of the rate in premature babies in the first few days of life.[6] In the present report we present the results of measurements of the urinary excretion rate of creatinine in a large group of well preterm and term infants.

Patients and methods

Altogether 84 24-hour urine collections were obtained from 60 infants, birth weight 800–4200 g, gestational age 27–40 weeks, and postnatal ages ranging from 3–68 days (table 1). Gestational age was estimated by a combination of menstrual history, ultrasound evaluation, and the clinical criteria of Dubowitz *et al.*[7] All the infants were in good condition at the time of study; none required mechanical ventilation or other major procedures and there was no evidence of any abnormality of renal function. Urine was collected by the method of Tarlow.[8] Adhesive plastic bags were carefully applied to the skin after painting with compound tincture of benzoin, which both protects the skin and improves adhesion. Care was taken to efface skin creases. A plastic tube was inserted into a hole in a dependent corner of the bag, the joint being sealed with epoxy glue. The other end of the tube was

Table 1 *Characteristics of infants studied*

	*No of observations**	*Mean (SD)*	*Range*
Postnatal age (days)	84	12·3 (12·0)	2–68
Postconceptional age (days)†	84	238 (23)	198–290
Weight (g)	84	1750 (660)	910–4200
Length (cm)	83	42·4 (4·5)	34–56·5

*A reliable length measurement was not obtained for one study

†Postconceptional age was calculated as the sum of gestational age and postnatal age on the day of study

connected to a collecting flask, the interior of which was kept at a slightly negative pressure relative to atmospheric by means of a Roberts pump. This ensured that the bag itself was empty almost all the time. Voiding was observed at the beginning and end of each collection period. The babies were inspected frequently for evidence of leakage, which was easily detected because of the system used; only complete collections were included in the study. Creatinine was estimated in urine by a kinetic (reaction rate) modification of the alkaline picrate method.[9] The results were analysed by correlation and linear regression.

The study was approved by the ethical committee of Guy's Hospital and the United Medical and Dental Schools of Guy's and St Thomas's Hospitals.

Results

The pooled, interassay coefficient of variation of the laboratory method for creatinine estimation was 2·6%. Histograms of the distribution of values for

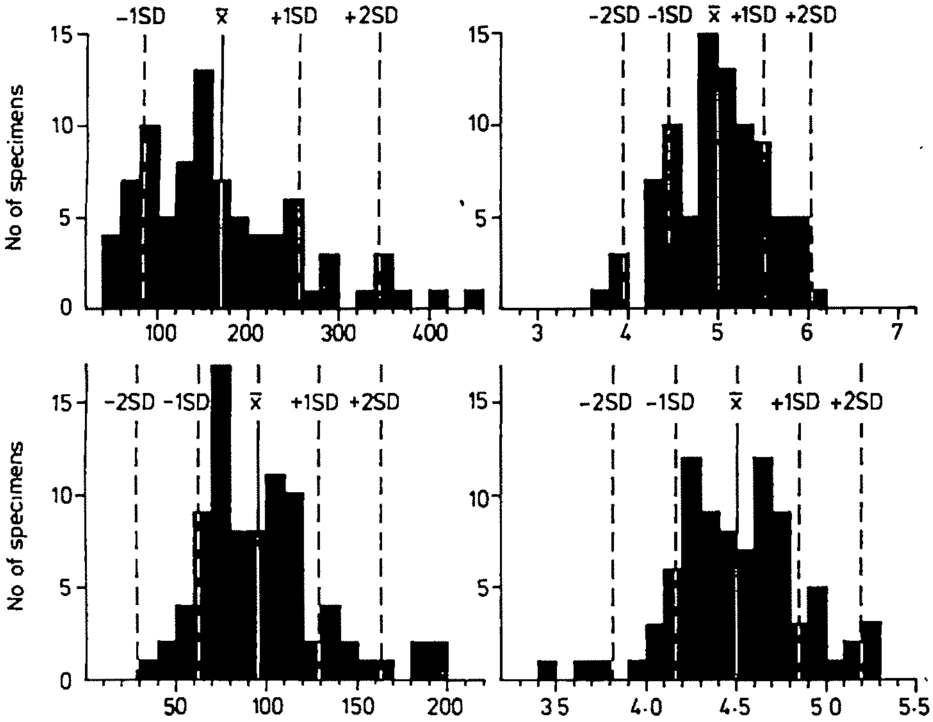

Fig 1 *Histograms showing the frequency distribution of urinary creatinine excretion expressed in μmol/day (upper panel, left) and in μmol/kg/day (lower panel, left). The right hand panels show the distribution of the natural logarithm (log_e) of the data shown in the left hand panels*

Table 2 *Correlation coefficients and regression statistics for the relation between 24 hour creatinine excretion and weight, length, postconceptional age, and postnatal age based on the linear regression equation y=a+bx*

Dependant variable *y*	*Independent variable* *x*	*Correlation coefficient (r)*	*p Value*	*Intercept* *a*	*Slope* *b*
Urinary creatinine excretion (μmol/day)	Weight (g)	0·72	<0·0001	2·02	0·09595
Urinary creatinine excretion (mg/day)	Weight (g)	0·72	<0·0001	0·23	0·01085
Urinary creatinine excretion (μmol/day)	Length (cm)	0·67	<0·0001	−381	12·98
Urinary creatinine excretion (mg/day)	Length (cm)	0·67	<0·0001	−43·1	1·47
Urinary creatinine excretion (μmol/day)	Postconceptional age (days)	0·69	<0·0001	−465	2·66
Urinary creatinine excretion (mg/day)	Postconceptional age (days)	0·69	<0·0001	−52·7	0·30
Urinary creatinine excretion (μmol/day)	Postnatal age (days)	0·001	>0·99	—	—

the urinary excretion rate of creatinine both uncorrected (µmol/day) and corrected for body weight (µmol/kg/day) are shown in fig 1 (before and after logarithmic transformation) Frequency distribution analysis showed obvious deviation from normality in the arithmetic plots of both variables, while the logarithmic plot gave a good approximation to normality; the median and logarithmic mean values were identical. The urinary excretion rate of creatinine (µmol/day) was positively and highly significantly correlated with weight ($r=0·72$, $p<0·0001$), length ($r=0·67$ $p<0·0001$), and postconceptional age (the sum of gestational and postnatal age, $r=0·69$, $p<0·0001$) but not with postnatal age ($r=0·001$, $p=NS$) (table 2, figs 2–5). In contrast, the excretion rate of creatinine factored by body weight (µmol/kg/day) did not correlate with weight ($r=0·1$[illegible], $p=NS$), height ($r=0·17$, $p=NS$), postconceptional age ($r=0·19$, $p=NS$), or postnatal age ($r=-0·07$, $p=NS$); the plot against postconceptional age is representative (fig 6). Over the range of data studied, the median (and logarithmic mean) value for 24-hour creatinine excretion was 90·4 µmol/kg/day with a normal range, defined as 2 logarithmic SD, of 45·4–179·5 µmol/kg/day (10·2 mg/kg/day, range 5·1–20·3).

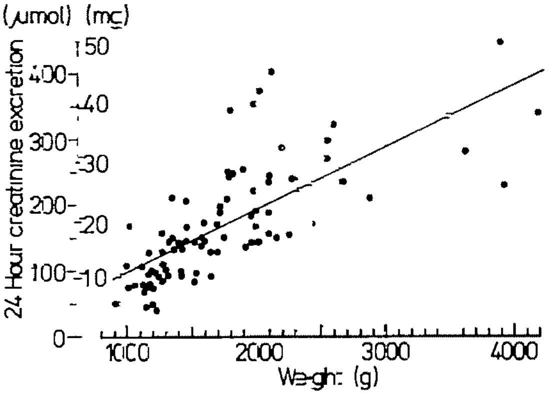

Fig 2 The regression of the urinary excretion of creatinine on weight The regression and correlation statistics are given in table 2

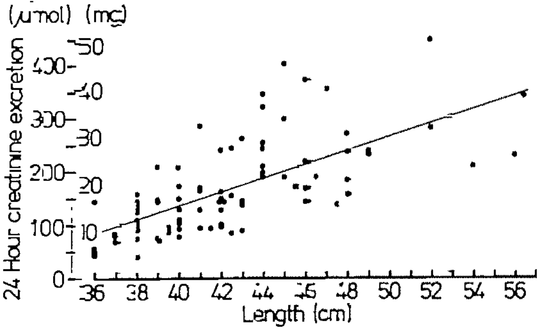

Fig 3 The regression of the urinary excretion of creatinine on length. The regression and correlation statistics are given in table 2.

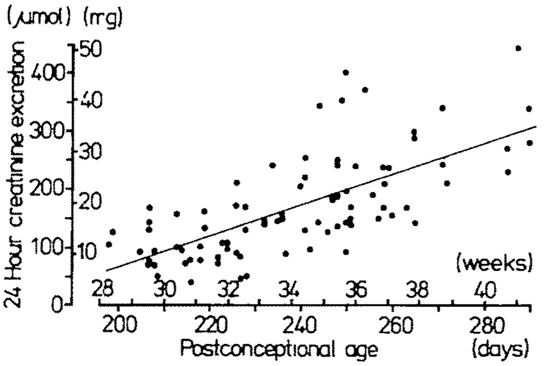

Fig 4 The regression of the urinary excretion of creatinine on postconceptional age. The regression and correlation statistics are given in table 2.

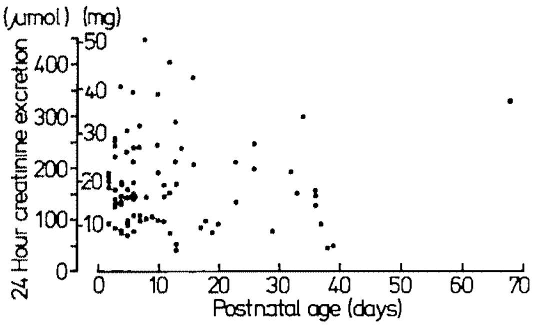

Fig 5 Urinary excretion of creatinine plotted against postnatal age There was no significant relation between the two variables (see table 2)

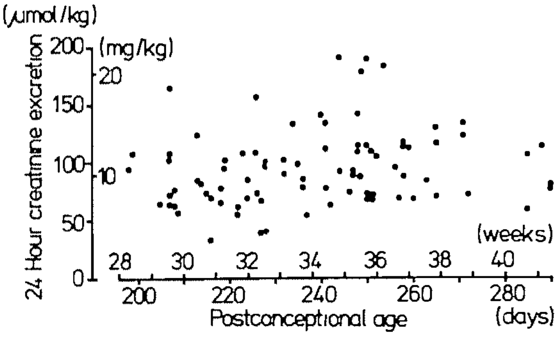

Fig 6 Urinary excretion of creatinine expressed per kg body weight, plotted against postconceptional age No significant relation was found ($r=0·19$, $p=NS$)

Discussion

Urinary creatinine is derived from muscle creatine.[10] Virtually all the body creatine is located in skeletal muscle and about 2% of this store is converted to creatinine daily and subsequently excreted in the urine.[11] In a steady state the excretion rate of creatinine must equal its production rate; it follows that the urinary excretion rate of creatinine is proportional to muscle mass. The urinary excretion rate of creatinine has been used in anthropometric studies as an indirect index of muscle mass since 1938,[12] and subsequent investigators have confirmed that it declines in malnourished children[13] and, with some limitations, that the creatinine-height index provides a measure of the degree of protein depletion or repletion in children in hospital.[3] The validity of the urinary excretion rate of creatinine in the measurement of muscle mass is the subject of a recent review.[4] It is therefore useful to know the limits of its normal range, in relation both to the investigation of body composition and in order that the excretion rate of other substances may be standardised to it.

We found that the urinary excretion rate of creatinine was positively correlated with weight, height, and postconceptional age but not to postnatal age. As might be expected, the correlation with weight was the strongest, but the three relations were remarkably similar, reflecting the association of these three developmental parameters with each other. Thus far, our findings are similar to those of Sutphen[6] but there are two important differences: firstly, the relation between weight and excretion rate was constant in our study at all weights and maturities examined. This is shown by the fact that the intercept (a) of the regression equation relating the urinary excretion rate of creatinine to weight is not significantly different from zero (table 2, fig 2), and (b) by the complete lack of any significant relation between height, weight, or postconceptional age and urinary excretion rate of creatinine factored by body weight (fig 6). In contrast, Sutphen predicted an output of 7·22 mg/kg (64 μmol/kg) at a birth weight of 700 g and 8·37 mg/kg (74 μmol/kg) at 1500 g; however, in the same paper he states that the standard error of the estimate of the urinary excretion rate of creatinine from weight was 1·26 mg (11·1 μmol). Thus these two estimates were separated by less than one standard error, even though lying close to the extreme values for weight examined in that study, and the difference cannot be regarded as even approaching significance. We studied a much larger sample across a considerably wider range of weight and maturity, which would be expected to make any such change with age or size more, rather than less, apparent and we conclude that infants of weight 900–4200 g and postconceptional age 198–290 days may be regarded as belonging to a single population with respect to excretion rate factored by weight.

The second difference between our results and those of Sutphen lies in the normal range of values found. As with most biologically derived data exhibiting a wide range of dispersion of values about the mean, our results conform more closely to a logarithmic than to an arithmetic distribution, the latter being significantly skewed to the right (fig 1). The urinary excretion rate of creatinine expressed per kg of body weight approximates well to a logarithmic distribution in that (a) the median value and the logarithmic mean coincide, and (b) the SD and 2 SD points cut the distribution curve symmetrically, with three observations falling outside each end of the 2 SD range. The best representation of the 'average' value, therefore, is the logarithmic (geometric) mean and the best representation of the normal range of dispersion of values the 2 (log) SD range, being roughly equivalent to the 3rd and 97th percentiles. Thus our mean value is 90 μmol/kg/day with a range of 45–180 (10 mg/kg/day, range 5–20). This is considerably different from Sutphen's average value of 71 μmol/kg/day (8·06 mg/kg/day); indeed, his maximum observed value was 84 μmol/kg/day (9·5 mg/kg/day), which is below our mean. The difference is not the consequence of the different ways the data were handled, as our arithmetic mean (SD) is even higher at 95·7 (33·3) μmol/kg/day (10·8 (3·8) mg/kg/day). Nor can it be due to the fact that our infants were, on average, studied at a somewhat greater postnatal age than Sutphen's, as there was no correlation between the urinary excretion rate of creatinine and postnatal age, contrary to the suggestion of Sertel and Scopes.[14] Differences in laboratory methodology are unlikely to be responsible as both studies used minor modifications of the Jaffe reaction, which is reliable at creatinine concentrations found in urine (although not necessarily in plasma at low concentrations). One possible explanation for the discrepancy lies in the fact that Sutphen seems to have factored by birth weight, while we used actual weight on the day of the study. The average age at the time of study in Sutphen's investigation was 7 days, when the babies were probably appreciably below birth weight, which would introduce an error as a consequence of dividing by a weight greater than that which actually obtained at the time. In a recently published study of glomerular filtration rate in newborn infants, Brion *et al* incidentally included some pooled data on the urinary excretion rate of creatinine[15]: the overall mean value obtained from 202 term and premature babies (calculated from data presented in their table 1) was 101 µmol/kg/day (11·4 mg/kg/day), a value almost identical to the arithmetic mean of our own observations Furthermore, in that study as in ours, there was little change in the excretion rate with age in either term or premature subjects.

We conclude that the urinary excretion rate of creatinine in preterm infants is positively correlated with weight, length, and postconceptional age, but is not influenced by postnatal age within the range of values studied. The normal range is 45–180 µmol/kg/day (5–20 mg/kg/day) with an average (logarithmic mean) value of 90 µmol/kg/day (10 mg/kg/day).

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Referrals to a regional neonatal intensive care unit

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SUMMARY Over a three year period 444 requests for the neonatal transfer of babies with acute medical problems were received at this regional neonatal medical unit. Despite an increase in available resources in the North Western Health Region the provision of intensive care remained inadequate with 38% of requests declined, and babies had to be referred elsewhere including to neighbouring health regions. The survival of those babies who had to remain at the hospital of birth (49%) was significantly lower than for those transferred to the regional centre (71%). Those babies declined admission had significantly lower gestational ages and birth weights than those accepted. For those babies with respiratory failure and birth weights of less than 1500 g within these two groups, however, there were no significant differences in birth weight, gestational age, or gender yet survival was significantly better for those transferred. Babies from multiple pregnancies caused particular problems if neonatal transfer was required.

We have previously drawn attention to the outcome for babies in the North Western Region who were declined admission to the regional neonatal intensive care unit at this hospital because the demand outstripped availability of accommodation.[1] During a 12 month period in 1979–80 we declined 65 (38%) of 170 requests for neonatal transfer of babies with acute medical problems The survival rate of those babies with respiratory failure who were declined admission and who had to remain in their local unit was significantly worse than those who were transferred.

Since that report the number of intensive care cots on our unit has increased from 10 to 15, and a subregional unit of six neonatal intensive care cots opened at Hope Hospital, Salford. Furthermore, paediatricians at certain district general hospitals in the region have been undertaking an increasing amount of neonatal intensive care.[2]

We now report the experiences of the regional neonatal intensive care unit over a consecutive three year period since these changes came about.

Patients and methods

From 1979 one of us (DGS) has kept a record of requests for neonatal medical transfer. From 1 January 1983 to 31 December 1985, each time a request was received by the neonatal registrar or consultant to transfer a baby to the regional neonatal intensive care unit at this hospital ('the regional centre') a form was completed giving details including the name of the referring hospital and paediatrician; date and time of the request; the name, sex, birth weight, gestational age, and date and time of birth of the baby. The reasons for requesting transfer were noted

The following definitions were used: (a) *impending or actual respiratory failure*· deteriorating respiratory distress or respiratory distress with superimposed apnoeic attacks, or recurrent apnoeic attacks alone, or ventilatory failure from birth, or prolonged ventilator dependence; (b) *deteriorating respiratory distress*: tachypnoea, thoracic cage retracion, or grunting worsening over the course of four hours, or accompanied by a progressive fall in arterial pO_2, blood pH, or a rise in arterial pCO_2; (c) *respiratory distress with superimposed· apnoeic attacks*· tachypnoea, thoracic cage retraction or grunting punctuated by episodes of apnoea; (d) *recurrent apnoeic attacks*: repeated episodes of apnoea without respiratory distress; (e) *ventilatory failure from birth*: a persisting need for positive pressure ventilation from birth because of inability to maintain spontaneous breathing; and (f) *prolonged ventilator dependence*: difficulty in weaning a baby from a mechanical ventilator as judged by the referring paediatrician.

If transfer was declined by the staff of the regional centre the reason was recorded according to the following criteria: (a) insufficient intensive care accommodation taking into account the predicted needs of high risk inborn babies during the forthcoming 24 hours, (b) insufficient essential items of equipment; (c) shortage of trained neonatal nurses; (d) medical staff unavailable to transfer the baby; (e) transfer not thought to be in the baby's best interests on medical grounds. Decisions to decline requests for transfer were made jointly between the senior neonatal sister on duty and the neonatal registrar or consultant, except for refusal on medical grounds, which was always discussed with the consultant.

At the end of each successive year of the study referring units were asked about the outcome for those babies declined transfer to the regional centre, whether they remained at their local hospital or were accepted elsewhere, and whether they survied or died.

The significance of data was analysed by χ^2 tests for comparison of proportions, and by Student's t test for comparison of means. Where appropriate 95% confidence intervals were calculated.

Results

During the three year period 444 requests for neonatal transfer were received from 23 maternity hospitals including six that were outside the North Western Region, and from one domiciliary birth. The mean (SD) of gestational age and birth weight of babies for whom transfer was requested was 30·5 (4·1) weeks (range 23–42 weeks) and 1566 (790) g (range 460–4440 g). Impending or actual respiratory failure was the reason for requesting transfer in 418 (94%) of babies. Other reasons were prematurity alone (n=9), perinatal asphyxia alone (n=3), congenital malformation (n=6) need for parenteral nutrition (n=4), renal failure (n=2), drug overdose (n=1), and local intensive care facilities already full (n=1).

Requests for transfer were declined in 170 (38%) of the 444 cases. The annual number of requests and the numbers declined are shown in table 1. Among individual hospitals that used the referral service at least four times during the study the frequency which their total number of requests for transfer was refused ranged from 17% to 57%.

Among the 170 babies who were declined admission a combination of criteria was responsible in 146 (86%) in as much as the unit was working to capacity in relation to the available intensive care cots, the number of trained nursing staff, and the availability of essential equipment such as mechanical ventilators and monitoring equipment. Ten babies (6%) were declined admission solely because of a shortage of trained nursing staff, and seven (4%) were declined because medical staff were unavailable to transfer the baby because another transfer was already in progress. Seven babies (4%) were declined transfer on medical grounds. Four of them had respiratory distress but were stable and were judged not to need intensive care at the time All of them remained at their local hospital and three survived. The baby who died suffered an intracranial haemorrhage and had been born to a mother with idiopathic thrombocytopenic purpura. One term baby had craniosynostosis and choanal atresia and was referred to a more appropriate specialist at another hospital where he later died. Two babies were felt to be too preterm to benefit from transfer; one remained in the local hospital and died, the other was transferred elsewhere and also died.

Table 1 *Requests for transfer 1983–5*

	1983	1984	1985	Total
No of requests	121	158	165	444
No (%) accepted	69 (57)	94 (59)	111 (67)	274 (62)
No (%) declined	52 (43)	64 (41)	54 (33)	170 (38)

Among the 393 babies in whom transfer was requested within 48 hours of birth 156 (40%) were declined admission. In contrast, 14 out of 51 babies (28%) were declined admission when transfer was requested after 48 hours of age. Among accepted babies, 19 (7%) were more than 7 days old compared with three (2%) among those declined ($p<0·05$). The 274 accepted requests included one baby who was transferred twice, seven who were so ill that they died before they could be transferred, and three who were not transferred because their condition suddenly improved immediately after the request for transfer was made. Therefore 263 were finally admitted to the regional centre.

Of the 170 babies who were declined transfer 135 (79%) were subsequently accepted at other units within the region, or at units outside the region (n=25). Three of these babies died before transfer could be effected The other 35 babies for whom intensive care was unsuccessfully sought remained in their hospital of birth (table 2).

The reasons for requesting referral for babies accepted at the regional centre and for those declined were similar (table 3). The birth weight, gestational age, and gender of babies who were transferred to the regional centre, transferred elsewhere, or who remained in their hospital of birth are shown in table 4. The mean birth weight and gestational age of babies who remained in their hospital of birth were significantly lower compared with those who were transferred to the regional centre.

The survival rate of babies until discharge home

Table 2 *Final result of referral request*

	1983	*1984*	*1985*	*Total*
No of babies accepted and transferred	68	90*	105	263
No of babies accepted but not transferred	1	3	6	10
No of babies declined but accepted elsewhere and transferred	40	49	43	132
No of babies declined, accepted elsewhere but not transferred	2	1	0	3
No of babies declined and stayed local	10	14	11	35

*One baby transferred twice

Table 3 *Reasons for referral requests*

	No (%) of babies accepted (n=274)		*No (%) of babies declined (n=170)*	
Respiratory failure:				
Deteriorating respiratory distress	135 (49·3)	(93·5)	94 (55·3)	(95·3)
Apnoea	17 (6·2)		9 (5·3)	
Respiratory distress and apnoea	34 (12·4)		19 (11·2)	
Ventilatory failure from birth	66 (24·1)		40 (23·5)	
Prolonged ventilator dependence	4 (1·5)		0	
Prematurity alone	7 (2·6)		2 (1·2)	
Asphyxia alone	1 (0·4)		2 (1·2)	
Congenital malformation	4 (1·5)		2 (1·2)	
Need for parenteral nutrition or long line	3 (1·1)		1 (0·6)	
Renal failure	2 (0·7)			
Drug overdose	1 (0·4)			
Local intensive care facilities full			1 (0·6)	

Table 4 *Birth weight, gestational age, and male:female ratio of referred babies*

	Mean (SD) birth weight (g) (range)	*Mean (SD) gestational age (weeks) (range)*	*Sex ratio (male:female)*
Accepted and transferred to St Mary's Hospital (n=263)	1620 (830)* (580–4440) Median=1380	30·8 (4·1)† (23–42) Median=30	158:105 (60%:40%)
Declined but transferred elsewhere (n=132)	1520 (700) (540–4000) Median=1400	30·3 (3·8) (24–40) Median=30	78:54 (59%:41%)
Declined and stayed at local hospital (n=35)	1330 (620)* (460–3000) Median=1100	29·3 (3·5)† (25–39) Median=29	21:14 (60%:40%)
Total requests	1567 (790) (460–4440) Median=1380	30·5 (4·1) (23–42) Median=30	266:177 (60%:40%)

*p<0·02, †p<0·025

(including those who died before transfer could be effected) was similar in those for whom request for transfer was accepted and those who were declined (70% *v* 66%). The survival rate of babies who remained at their hospital of birth (49%) was significantly lower than those who were transferred to the Regional Centre (71%) and those who were transferred elsewhere (73%) (p<0·025).

Among babies with respiratory failure the incidence of the various types of presentation was similar in those who remained in their hospital of birth and those who were transferred to the regional centre. Those remaining in their local hospital, however, had a lower mean birth weight (table 5). The survival rate of those with respiratory failure who remained in their hospital of birth (47%) was significantly lower than those who were transferred to the regional centre (72%) (p<0·01). Babies with respiratory failure and birth weights of below 1500 g who were transferred to the regional centre or remained in their hospital of birth were also compared. The survival rate for those transferred (141) was 64% and for those remaining locally (22) was 36% (p<0·05). There were no significant

Table 5 *Comparison between those babies with respiratory failure who were transferred to the regional centre and those who remained in their hospital of birth*

	No (%) of babies transferred (n=246)	*No (%) of babies who stayed locally (n=32)*
Reason for referral:		
Deteriorating respiratory distress	128 (52·1)	17 (53·1)
Respiratory distress and apnoea	34 (13·8)	4 (12·5)
Apnoea alone	17 (6·9)	1 (3·1)
Ventilatory failure from birth	63 (25·6)	10 (31·3)
Prolonged ventilator dependence	4 (1·6)	0
Mean (SD) birth weight (g)	1610 (800)	1330 (620)*
Mean (SD) gestational age (weeks)	30·5 (4·0)	29·3 (3·5)
Sex ratio (male:female)	148:98	19:13
Survived	177 (72·0)	15 (46·9)†

*p<0·05. †p<0·01.

Table 6 *Outcome of requests to transfer multiple births*

	Babies accepted at regional centre (n=14)	*Babies accepted elsewhere (n=27)*	*Babies who remained locally (n=7)*	*Total (n=48)*
Mean (SD) birth weight (g)	1490 (610)	1420 (570)	1060 (400)	1390 (570)
Mean (SD) gestation age (weeks)	30·0 (2·1)	30·2 (3·1)	27·1 (2·0)	29·7 (2·8)
Sex ratio (male:female)	7:7	15:12	6:1	28:20
No (%) survived	12 (85·7)	16 (59·3)	3 (42·9)	31 (64·6)

differences in birth weights, gestational ages, or gender between these two groups.

Babies who were the products of multiple pregnancies accounted for 48 (11%) of the requests for transfer (table 6). Only 14 (29%) were accepted for transfer to the regional centre. These 14 babies had a lower birth weight but similar gestational age compared with other accepted babies. Their survival rates was 86%. Five sets of twins were accepted and four single babies when a request was made to take only one of a pair. Eight sets of twins were declined and of these, four pairs were later split and accepted elsewhere. Thirteen single twins, one of a set of triplets and all four of a set of quadruplets were also declined admission. Babies of multiple pregnancies who were not admitted to any intensive care unit were smaller and significantly less mature than those accepted. They had the lowest survival of any group considered here (43%).

Discussion

Many factors, not considered in this study, influence the work load of a regional referral centre and thereby determine the extent to which requests for transfer can be accommodated. For example, during the period of this study the number of babies admitted to the neonatal medical unit after in utero transfer rose from 32 in 1983 to 69 in 1985. Babies with birth weights of 1000 g or less demand a disproportionate amount of resources. In 1983, 43 such babies were cared for on the unit, rising to 68 in 1985. In addition, the North Western Regional Health Authority has predicted a rise in the region's total births from 53 100 in 1981, to 56 000 in 1986, and 62 000 in 1993.

Whereas we reported in an earlier study that 42 babies in a 12 month period were declined admission and had to remain at their hospital of birth, the current study showed that only 35 babies in three years had to remain locally.[1] The mortality of those babies who remained at their hospital of birth, however, was still significantly higher compared with those transferred suggesting that unnecessary deaths are still occurring. The new neonatal referral service based at Hope Hospital, Salford accepted between 50 and 65 neonatal referrals annually during this study, many being primary referrals to that unit. Yet despite this, and despite and increase in size of the existing referral centre at this hospital, 25 babies that we know of had to be transferred to other health regions for intensive care at great inconvenience to parents. The circumstances that make it necessary for a neonatal intensive care unit to decline further admissions often persist for several days. District hospital paediatricians are aware of this and might make direct extra regional referrals without trying to contact their own regional centre. We suspect that some district paediatricians, despairing of previous unsuccessful attempts to secure the admission of babies to their regional centre, cease to request referral of babies requiring intensive care, and instead do the best they can locally. Our current system of documentation does not register such cases.

It was not the purpose of this paper to compare in detail the quality of neonatal care according to whether babies were accepted or declined at the regional centre. The data do not allow that. It cannot go unnoticed, however, that the mortality of ill babies who were unable to be accommodated at the regional centre or elsewhere was significantly higher than those babies who were transferred. Those babies who remained at their hospital of birth had a similar pattern of illness to those who were transferred, but they were rather smaller and more immature. When intensive care is offered to an extremely preterm baby resources are committed to one patient for many weeks or months, whereas those resources might be used in the same period of time by several more mature babies each needing only a week or two of intensive support. It is possible that the bias towards smaller and more immature babies among those who remained in their hospital of birth might be due to selection in so far as when space is limited in the regional centre more mature infants may get preference. If a request for transfer of an extremely small preterm infant is declined the referring paediatrician may not continue to try other referral centres.

Requests for the transfer of babies of multiple pregnancy generate special problems. Practical difficulties arise in the actual transfer of two or more babies and it may only be possible to accept one baby for transfer and care. Which baby should it be? The remaining babies may be offered no support, or transferred to another unit miles away creating major problems with respect to parental visiting. These important considerations remain unresolved.

Indications for transfer and the reason for refusal remain broadly the same as in our earlier report.[1] Accepting a neonatal transfer commits the unit to caring for the baby for as long as is necessary and this may be for weeks or months. Excellent standards of care must be offered to all babies accepted and we do not accept the 'pack in as many as you can' philosophy. Indeed, at times it may be necessary to shut cots in order to maintain standards with resource shortages. Adequate numbers of skilled nurses are mandatory for the safe running of a neonatal unit. We found in this study as before that a shortage of nurses was often a part reason, and sometimes the sole reason for declining a transfer request.[1] We suspect that at times skilled nursing staff may be subjected to extreme emotional pressures regarding neonatal transfer requests. When the unit is working to capacity, if they suspect that a baby will die unless transferred they might agree to take on more work than is desirable for the safety of the unit.

We thank Dr M Robinson and Dr G Hambleton for the data regarding Hope Hospital, Salford

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Clinical features of conversion disorder

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SUMMARY This study reviewed the case notes of 52 children diagnosed as suffering from hysterical conversion during admission to a paediatric teaching hospital over a 10 year period. The disorder was rare below 8 years of age and girls outnumbered boys three to one. Altogether 75% of the children presented during spring and summer; at the time of end of year exams and the beginning of the new school year. The presentation was usually polysymptomatic with gait disturbance being the main complaint in 36 children. Sensory abnormality, predominantly pain, was present in 40 children; this indicates a strong association between psychogenic pain and conversion disorder in children. At discharge 32 were completely recovered or had appreciably improved. There was a core group that presented particular difficulties with diagnosis and showed little positive response to treatment.

Hysteria persists despite changing social structures and by attempts to define[1-3] or dispose of it.[4] The diagnosis can be an unrivalled test of a clinician's skill and belief in his judgment. Certainty is demanded and mistaken diagnosis threatens the doctor with exposure to the resentment of the patient and his or her family, the righteous censure of colleagues, and to humiliating and costly appearances in courts of law.[5] Even in the most obvious case the diagnosis is seldom made without a certain uneasiness and reluctance

Hysteria in childhood poses special problems as it is intimately concerned with the child in the family Taylor has written extensively on the psychiatric aspects of childhood hysteria and sees three elements in its emergence.[6 7] The child is oppressed by a predicament that is perceived as intolerable and from which there seems to be no escape Relief appears in the form of a claim to illness that is managed and promoted by an ally: usually one or both parents. The final element is a model for the illness that may be obvious or obscure or may evolve during the child's dealings with doctors. This structure provides a means for recognition of the psychological forces at work but Taylor uncouples the psychological and the physical, seeing them as different independent 'domains' of the individual's existence. The emergence of organic disease is not seen as invalidating the hysteria.

This formulation, helpful as it is, in some ways provides rather cold comfort for the paediatrician dealing with a child who may be hysterical. Total exclusion of organic disease is usually demanded by parents (and often by psychiatrists) before psychiatric treatment can start Additional misgivings arise from the notion that there is an infinite variety of manifestations of hysteria. Older studies of childhood hysteria are often not helpful as diverse entities such as anorexia, hypochondriasis, abdominal pain, headache, and anxiety were included alongside cases of conversion reaction.[8 9] More recent studies have tended to be of small samples[10 11] or principally to approach the subject from the psychiatric[12-15] or neurological viewpoint [16] There are very few long term follow up studies.[8 17 18] Caplan reviewed 28 children referred to the Maudsley Children's Hospital with a provisional diagnosis of hysteria.[17] Thirteen were found to have organic disease referable for the original complaint. In 10 children, however, this was discovered before the child left hospital. Caplan felt that after careful neurological and psychiatric assessment a group of 'true hysterics' could be identified who do not have organic disease and may do well in the long term Stevens reached similar conclusions [18] In both series the children initially presented in the 1950s and early 1960s long before the availability of computed tomography and the other sophisticated techniques of neurological investigation available today.

Study method

The aim of this study was to examine the clinical features of a group of carefully defined children admitted to a general paediatric hospital in whom the diagnosis was made only after detailed examination, investigation, and psychiatric assessment. The study was limited to children with conversion disorder as this is the most common and most easily defined presentation of childhood hysteria. A search of the medical records of all children discharged from the Royal Alexandra Hospital for Children over the years 1975–84 with a diagnosis of conversion reaction or hysteria was performed. The notes were examined and found to be surprisingly detailed. In particular the more difficult cases exerted a morbid fascination on those looking after them. Long, often revealing, entries appear from medical, nursing, and paramedical staff. Those cases that satisfied the Diagnostic and Statistical Manual of Mental Disorders[3] criteria for conversion disorder were studied. These criteria are as follows.

1. (1) The predominant disturbance is a loss of or alteration in physical functioning suggesting a physical disorder.
2. (2) Psychological factors are judged to be aetiologically involved in the symptom, as evidenced by one of the following:
   - (a) there is a temporal relationship between an environmental stimulus that is apparently related to a psychological conflict or need and the initiation or exacerbation of the symptom;
   - (b) the symptom enables the individual to avoid some activity that is noxious to him or her.
3. (3) It has been determined that the symptom is not under voluntary control.
4. (4) The symptom cannot, after appropriate investigation, be explained by a known physical disorder or pathophysiological mechanism.
5. (5) The symptom is not limited to pain or to a disturbance in sexual functioning.
6. (6) The symptom is not due to a somatisation disorder or schizophrenia.

Sixty four children and adolescents had a discharge diagnosis of conversion reaction or hysteria. Twelve patients were excluded: eight failed to meet the criteria and were suffering from hysterical fugue states, anorexia nervosa, or conduct disorder. Two had pain only, and in two others the notes were incomplete. This left 52 patients of whom most were admitted under the care of a general paediatrician. Formal psychiatric assessment was performed in 47 cases (90%), 27 patients were assessed by a paediatric neurologist, and 16 were examined by one or more of the authors.

Results

The mean age of the 52 children was 10 years with a range from 6 to 15 years; 32 (62%) were in the 10 to 12 age group (figure), and 39 (75%) were girls. Regarding birth order: eight were the only child, 14 were first born, 15 were second born, and 15 were born third or later in the family. During the course of their illness 28 had a single admission and 12 required multiple admissions. Two children had two quite distinct hysterical episodes separated by a number of years. There was an apparent seasonal variation with 27 children admitted in the three months of (Australian) spring and 39 in all admitted in the spring and summer (table 1).

CLINICAL FEATURES

Before admission 22 children had symptoms for less than a week In 19 the complaint had been present

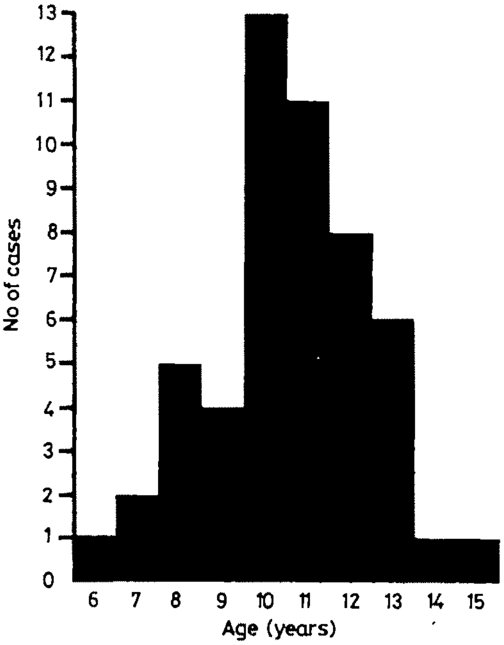

Figure *Age at admission to hospital*

Table 1 *Time of year at admission to hospital*

Month of admission	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
No of cases	5	6	4	1	5	3	—	2	7	11	9	1

for more than a month, and in some of them for more than a year. The presentation was polysymptomatic in 32 children and the presenting symptoms are divided according to the function most disabled.

(1) Abnormality of gait

Altogether 35 children had presented with abnormality of gait. Of these, 16 complained of difficulty in, or total inability with walking because of generalised leg pains. The remainder had more classical 'pseudoneurological' presentations. Nine had monoparesis of a lower limb, three were paraplegic; two hemiplegic; two had gross ataxia; two had generalised tremor, and two walked in a shuffling bent over fashion. In all but three children pain and, less frequently, anaesthesia were prominent features. The affected limb(s) was often not troublesome at rest but any attempt at examination or movement provoked complaints of intense pain often accompanied by tears.

(2) Others

Eight children had pseudoseizures; two painful monoparesis affecting the upper limb; three blindness (pain being a feature of each); two sneezing; one aphasia (with ataxia); one stridor, and one globus hystericus.

Overall, 40 (77%) complained of pain, parasthesia or anaesthesia, or both, as well as loss of function. Pain was by far the most common complaint. Besides the three children who principally presented with blindness, eight others had visual complaints—for example, blurred or double vision. In one child presenting with blindness there may have been underlying mild optic neuritis but the bulk of the complaint was thought to be hysterical.

Six children had organic disease before their hysterical episodes. Two had diabetes, one severe eczema, one Silver-Russell dwarfism, one epilepsy, and one congenital cataracts and glaucoma. Another was found to have choreiform movements that had been present all her life but no diagnosis had been made previously. In only two children did the conversion symptom affect the part of the body already identified as abnormal.

The psychological features of the children are presented in table 2. One child had been sexually abused by her grandfather well before her hysterical episode. This possibility was considered in three other children but had not been proved at the time of discharge.

Thirty families (58%) were anxious and the home environment was pervaded with fears of loss and physical illness. In contrast, 11 families (21%) were grossly disrupted, with parents and children in open conflict. Divorce or separation of the biological parents had occurred in 12 families (23%).

Table 2 *Psychological features of the 52 children*

Feature	*No (%)*
Presence of a model	28 (54)
Recent stressful life events	24 (46)
Threat of separation or loss of relative	24 (46)
History of similar symptoms of psychiatric illness	17 (33)
La belle indifference	10 (19)

INVESTIGATIONS

In general clinical investigations had been performed, even in those cases where conversion reaction seemed highly likely. Most children had 'routine' blood tests—for example, full blood count and electrolytes. Erythrocyte sedimentation rate (in 28), antinuclear factor, rheumatoid factor, and titres for Epstein-Barr virus, cytomegalovirus, and mycoplasma were often requested. Twenty four children had radiographs of the affected limb, skull, or chest. Eleven had electroencephalograms taken, nine had computed tomographic scans, nine had radioisotope studies, and 10 had lumbar punctures (including four myelograms taken). Two children had arteriograms taken of the lower limbs; two had bronchoscopies; three had nerve conduction studies; two had edrophonium tests; two had visual evoked responses tested; one had a barium enema, and in one single patient bone, muscle, and skin biopsies were performed.

Difficulties arising from interpretation of the investigations and true organic changes resulting from prolonged disuse of a limb meant that they clouded rather than clarified the problem in a number of cases. Both arteriograms were performed after radioisotope flow studies suggested obstruction to the arterial supply of the lower limb. In seven of the 11 children who had electroencephalograms minor abnormalities were present. Seven with painful limbs had abnormalities shown on their radiographs such as osteoporosis or joint narrowing. The most difficult case in the entire series was treated with steroids at another hospital for dermatomyositis on the basis of weakness and patchy myopathic changes shown on an electromyogram. When she failed to respond the steroid dosage was increased, and this combined with her near total immobility resulted in appreciable metabolic derangement and steroid myopathy. It was only after a month at this hospital and a massive number of investigations and extensive consultation that it was considered that her illness was primarily psychological.

On a number of occasions the investigation resulted in an escalation of the symptoms. One girl became paraplegic after her barium enema, and others complained bitterly of back pain after lumbar puncture. In one girl subjected to arteriography of her lower limb the procedure was performed at a time when she had begun to improve and produced a return of her earlier symptoms

COURSE OF ILLNESS

A number of children had been treated elsewhere before referral to this hospital. Four children had been treated with corticosteroids. In two this was used for intractable sneezing, in one for 'dermatomyositis', and in one for stridor in which an asthmatic component was suspected. Four children with pseudoseizures were treated with anticonvulsants; a variety of anti-inflammatory agents were used for the musculoskeletal symptoms. One child with persistent leg pain had been unsuccessfully treated with one month of immobilisation in plaster on two separate occasions and had also received intra-articular cortisone injections.

In hospital those children who did not spontaneously and rapidly recover were generally treated by the method previously described by Gold[10] and Dubowitz and Hersov[11]· this consists of stopping unwarranted investigation, giving the child physiotherapy and occupational therapy, and paying attention to psychological factors. Three children had psychotropic drugs prescribed by the department of psychiatry. One child was prescribed imipramine for depression. Both children with intractable sneezing were treated with haloperidol because it was thought that their symptoms resembled a tic. Neither had any other feature of Tourette syndrome nor responded to the medications.

In 23 children, the symptoms had completely resolved at time of discharge. Nine children showed a noticeable improvement in their symptoms, 13 a moderate improvement and eight none. In one case the child's condition at the time of discharge was not recorded. Those children with a shorter duration of symptoms before admission tended to recover more quickly, but this was a trend rather than a strict relationship.

THE 'DIFFICULT' GROUP

A subgroup of 13 children, 11 of them girls, presented particular problems with both diagnosis and management. Their symptoms had been present for a long time at admission: 10 being affected for more than two months Even more than in the rest of the sample, many organ systems were affected. Nine had weakness combined with nausea, lethargy, and head, limb, and abdominal pains. In four of them weakness of a limb was accompanied by severe localised pain. They often looked ill and seemed depressed. Anorexia was a feature, with considerable weight loss occurring in a third. They were generally 'good' children, serious minded, compliant, and perfectionistic, who came from families with high expectations of them and were anxious about illness. Seven were at the top of their class or were the local athletic champion. They spent a long time in hospital, up to 72 days, with an average stay of 31 days. Most of the invasive investigations were performed on them, and during their stay doubts about the diagnosis continued. Once treatment began their response was frustratingly slow despite intensive efforts Only two of these 13 children had substantially improved at discharge; four showed no change at all.

Discussion

There is an impression, supported by many authors, that the manifestations of conversion reactions are protean.[1 19] This group, on the contrary, displayed many common features: female predominance, a narrow age range, presence of pain or anaesthesia, and presentation with gait disorder. So called classical presentations such as globus or blindness were relatively rare.

The excess of female patients over males is a feature of adult hysteria but has also been seen in many previous paediatric studies[8–10 14–16 18] The narrow age range at presentation is probably artefactual with children older than 13 being referred to adult hospitals. The important point is that there were only three children under the age of 8 years and none under 5 years. The dangers of the diagnosis of conversion disorder in the young child cannot be overstated and are well documented.[20]

Given that children in whom pain was the sole or predominant symptom were excluded from the present study (they were regarded as suffering from psychogenic pain disorder) the frequency and severity of pain as an associated symptom was striking. Altogether 40 (77%) complained of pain or sensory disturbance. This, with the required loss of function, principally an inability to walk, made the child's declaration of illness inescapable The child was prevented from getting about; this ensured a reaction from the parents. It fits well into the concept of the child 'talking with his body'.[21] The observation that pain is a frequent concomitant of conversion has previously been noted by Gold[10] and Schneider[16] and Sheffield.[22]

An interesting finding is the apparent seasonal incidence, with 50% of the group presenting in the spring. Many of these children were chronically stressed but a number of factors can be advanced as precipitants of admission at that particular time. Spring is the time of the end of year school exams in Australia An incapacity to face failure has been long regarded as an important aetiological factor in the production of a conversion reaction.[23] This is further supported by virtual absence of cases during the December school holidays and then an upsurge in January and February at the beginning of the new school year. Additional factors in spring include increased pressure on the child to take part in outdoor sporting and recreational activities that may uncomfortably highlight deficiencies in skills and bodily maturation compared with peers. There may also be an intensification of feelings revolving around the beginnigs of sexual maturation.

These children were heavily investigated. It is impossible from a retrospective study to say how many tests may have been avoided. Appropriate clinical investigation is one of the diagnostic criteria for conversion disorder and routine investigations have an important role in convincing the child and the child's allies that physical disease is not present. At times investigations had the opposite effect: the detection of minor abnormalities undermining rather than consolidating the diagnosis of psychological illness and precipitating a further round of investigation. Pressure for additional and often more invasive investigations arose and the institution of appropriate treatment was delayed. Sometimes the investigation provoked a worsening of the child's condition.

Two broad patterns of psychological disturbance appeared in the families. Firstly, there was a group that consisted of anxious families preoccupied with, yet fearful of, disease where illness was the prevailing means of communication. In one such family the little girl kept 'graves' marked with a cross for her cat, budgerigar, and both grandparents in the backyard. Her mother's only close friend had a child who had recently died of leukaemia. She was the youngest child and the mother would keep her home from school at the slightest premonition of illness. In another family, the father was a miner and each morning he would line up the mother and children and kiss them goodbye in case he was killed during the day's work. This sort of family often initially seemed 'normal' and tended to produce the most difficult cases. Secondly, there was a pattern of chaotic social circumstances that was exemplified by a family where the mother herself was the 'black sheep' of her family. She had three families with seven children from different alcoholic fathers. The index case, a 13 year old girl, presented with pseudoseizures, her brother was described as a 'young sociopath', and her sister was unmarried, pregnant, and 'antiestablishment'. In another family the parents argued openly and constantly at home, and the father continually threatened to leave to live with his girlfriend. He had attacked his wife after a visit to a local club and forced her to walk home dressed only in her underclothes. Despite their estrangement he had split open the head of his wife's boyfriend with a wooden pailing. The presenting symptoms in these children were usually more obviously 'hysterical' and the diagnosis more easily made.

A model was identified in only 28 (54%) of the group. This relatively low figure partly stems from the retrospective nature of the study but also, as Taylor warns,[7] the model may arise from the long forgotten past or be stumbled upon in the course of the patient's encounters with the medical profession. The virtual absence of sexual abuse almost certainly reflects the lack of awareness of its frequency that prevailed for most of the years of the study. Even in the last years when it was actively looked for no definite cases were found.

The treatment given before arrival at this hospital shows the dangers when allies include doctors. The most dramatic example was the treatment of one child with hysterical sneezing: a 10 year old girl from a country town, who was the captain of her class at school. She was referred after two weeks of constant sneezing day and night. This was felt to be 'probably hysterical, but she appeared well adjusted, sensible and cooperative and the parents uncomplicated and also sensible.' Over two weeks treatment with promethazine, pentobarbitone, thioridazine, morphine, sodium cromoglycate, beclomethasone, and prednisone were tried with respite from the sneezing only during the hours of sleep. She was then taken to the operating theatre and had submucosal diathermy and antral washout to 'shock' her out of it. When this failed she was transferred

The important aspects of the treatment in hospital included the use of the team approach provided by paediatricians, psychiatrists, and paramedical staff. The provision of an 'escape with honour' was essential. Twenty one children (40%), however, did not show an appreciable improvement at discharge There are a number of reasons for this Some children were returned to their referring doctors after diagnosis without beginning treatment. Also being in hospital may reinforce illness behaviour The identification of a problem as psychological is unlikely to persuade the child suddenly that all is well if there has been no change in circumstances and may even result in an amplification of the patient's sypmtoms in an effort to 'prove' their organic basis. Certainly taking a punitive line and keeping the child in hospital until the symptoms disappear invites a degeneration into a contest of wills between the patient and the doctor.

In many of the children it was relatively easy to decide that no organic disease was present. For example, the little girl with intractable sneezing stopped on request so an artefact free electroencephalogram could be obtained and the sneezing immediately recommenced on its completion. A boy who was apparently paralysed and in a wheelchair was seen to kick a ball across the room. The 13 children who formed the difficult subgroup provided no such help. The presence of weakness, generalised limb pains, weight loss, and depression posed a wide differential diagnosis including malignancy and collagen vascular disease. Many were gaunt and miserable and seemed to be chronically ill. Ten children had had symptoms for more than two months before their admission, and when diagnosis was made they responded very slowly to treatment. Allies were readily recruited: there were entreaties such as 'surely an angiogram is indicated' appearing not infrequently in the notes from the more junior medical staff. Other staff found them obstinate and frustrating 'burping, inactive, wingeing, bored . . .' They were generally high achievers under strong pressure from the family to succeed at school and at sport. The illness provided relief from their obligations without the expression of open rebellion. Despite their long admissions only two were substantially improved at discharge. Briquet's words of over 120 years ago seem disturbingly appropriate.[24] 'No illness is more difficult to cure than hysteria. . . . One quarter never recover or have the illness their entire lives. Some young girls who become hysteric before the age of 12 or 13 years are condemned to a lifetime of suffering, malaise and sometimes serious illness. They may spend a year or more in bed, completely incapacitated. They are always sick, abort easily, or if they go to term, give birth to more hysterics.'

Much can be made of the role of excessive investigation, contradictory medical opinions, and failure of early recognition of the problem in this sort of prolonged course. It may be equally argued that these children were sicker, their predicament worse, their allies stronger, and their nature more obstinate. Follow up is available on a number of them. The most severely affected girl who, after 72 days in hospital, was still unable to use her hands and would eat by putting her mouth to her plate, took part in a seven hour 'skatethon' several months later. Another immobile and debilitated girl was sent to her brother's property in the country where among the relatively primitive facilities she refused to take her antidepressant medication and made a complete recovery. This sort of cure can be related to a change in the structure of a predicament. Forty seven years ago Sheldon advocated two weeks convalescence by the seaside as part of the treatment of childhood hysteria.[25] As Taylor says: 'It is not necessary, as it were, to remove the last straw that broke the camel's back in order to get the creature back onto his feet; any straw might do.'[6] Perhaps in these apparently intractable cases early removal from hospital should be aggressively pursued.

The final question remains, as always, that of organic disease. No formal follow up has yet been attempted on this group. From the experience of Caplan[17] and Stevens[18] we would anticipate a low incidence of organic disease. In the time of the study one child returned with symptoms suggestive of temporal lobe epilepsy that were quite distinct from her initial conversion symptoms. No other cases appeared. It is of course possible that the return was to another hospital.

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Psychological effects of day case surgery compared with inpatient surgery

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SUMMARY Short term psychological disturbance in 70 children undergoing minor surgery was compared in two randomly allocated groups by means of questionnaires answered by their parents. Significantly less psychological disturbance was reported in children undergoing day case surgery compared with children admitted on the day before and discharged on the day after surgery. Children who had day case surgery were less often reported to require extra attention in the first week after discharge home, and at three months after operation these children were less often said to be still affected by their hospital stay. It is concluded that a reduced psychological upset can now be added to the other arguments in favour of day case surgery in children.

Treatment of children in hospital as day cases rather than inpatients has been advocated since the beginning of the century,[1] and now up to 50% of general surgical operations in children are done in this way.[2] Several arguments can be put forward in favour of this. Arguments of a clinical nature are earlier ambulation, leading to a possible decrease in morbidity, and the reduced risk of cross infection. Other arguments are lower cost of day case treatment, greater convenience for parents, and lastly but perhaps most importantly, reduced psychological upset of the child.

Fletcher has reviewed the whole question of psychological disturbance of children after admission to hospital.[3] The existence of long term psychological upset after childhood admission to hospital was shown by Douglas in a large scale retrospective study of conduct disorder and emotional disorder in adolescents[4]; this was confirmed by Quinton and Rutter.[5] In the shorter term, exact definition of psychological upset is difficult, but eating problems, sleeping problems, enuresis, regression to earlier levels of functioning, and anxieties about hospitals and illness are usually taken as indications of an adverse effect. Trials have been carried out to test various procedures in attempts to minimise psychological upset in children admitted to hospital, these trials have supported measures such as parents remaining with their children in hospital[6 7] and reduced length of hospital stay.[8] On the whole, however, such trials have not been randomised. One exception is a trial by Von Troschke on children undergoing strabotomy, where a two day hospital stay with the mother staying in hospital was shown to produce less behavioural disturbance than a 10 day stay with only restricted visiting.[8]

We report a randomised trial in which children undergoing a general surgical operation were randomly allocated either to be admitted as day cases or to be admitted to hospital for two nights.

Subjects and methods

Subjects admitted to the study were children referred to the outpatient clinic, aged 9 months to 6 years, with no previous hospital admissions, and who required routine hospital admission for minor general surgical operations under general anaesthesia.

The children were randomly allocated to two groups—either to be admitted and discharged on the same day as the operation ('day cases') or to be admitted on the day before, and discharged on the day after the operation ('inpatients'). Randomisation was by drawing of a card from a prerandomised pile Visits by a district nurse were arranged for all children to start on the day after discharge. Questionnaires were supplied to the parents and were to be completed on three occasions—before operation, one week after admission, and three months after admission Each questionnaire contained about 100 questions covering the child's behaviour and response to the operation and several related matters. Some questions in the questionnaires were taken from standard questionnaires of child behaviour; the results of these questions are not reported here, but it is hoped to report them elsewhere. There are, however, no standard questionnaires specifically designed to determine adverse psychological effect on children from admission to hospital. Some questions were therefore devised especially for this study, and this was done on the basis of responses made in an open ended interview by a pilot sample of six parents not included in the subsequent study. For the purposes of the present report, responses to several important questions in the second and third questionnaires have been analysed. For each question in the questionnaires the parents were required to select from a small number of possible answers—for example, 'How much extra attention has s/he needed since the operation: a lot, some, or not very much?'

The main questionnaire (one week after operation) was sent to the parents of 70 children and was returned in 65 cases, (response rate 93%). The questionnaire sent at three months after the operation was returned for 62 of these 70 children (response rate 89%). Response rates for individual questions were in some cases slightly less. The children for whom data were not available did not differ in age, type of operation, or complication rate from the rest.

Seven children were inadvertently admitted or discharged on the wrong day (one of the day case group and six of the inpatient group). Data were available on all of these seven. Except for a preponderance of the inpatient group, these seven did not differ in any apparent way from the rest of the sample. Analysis of the data has been carried out both including and excluding these seven patients with no appreciable effect on any of the results of the study. It is therefore concluded that no error has been introduced by these breaches of protocol.

In a further seven cases it was necessary to override the protocol for medical reasons. In each case the child was kept in hospital for an extra 24 hours for a reason such as vomiting after the general anaesthetic or delay in micturition after a circumcision. Again, analysis of the data has been carried out both including and excluding these seven patients and again none of the results is affected. The data presented in the results section are for those 58 children (83%) for whom the protocol was accurately followed (except where medical reasons made this impossible) and for whom the questionnaire at one week after operation was returned.

Of these 58 patients, 35 were admitted as day cases and 23 were admitted as inpatients. The mean ages on admission for the day case and inpatient groups were 3 years 9 months and 3 years 4 months, respectively (overall range 9 months to 6 years 10 months). The two groups were also comparable for sex, operation, and complication rate. Roughly half of the children were circumcised, a quarter had a herniotomy performed, and the rest underwent a variety of procedures such as removal of a mass or cystoscopy. Four children developed complications—two inguinal wound infections and two scrotal haematomas—of which one was in the day case group and three were in the inpatient group (the difference was not significant).

The two groups were also comparable for the parents' assessments of amount of pain experienced after discharge, degree of difficulty in micturition, and amount of upset during dressing of any wound.

The significance of differences found was assessed using the χ^2 statistic with Yates's correction where appropriate.[9] Significance was taken to mean $p<0{\cdot}05$.

Results

Children treated as inpatients were found to be more affected by their hospital stay than children treated as day cases. At one week after discharge parents reported that eight of 23 inpatient children had 'needed a lot of extra attention since the operation' compared with one of 35 day case children ($\chi^2=10{\cdot}9$, $p<0{\cdot}01$). The trend was still present at three months but was no longer significant ($p=0{\cdot}2$). Furthermore, at three months five of the inpatient children were still affected by their hospital stay in their parents' opinion compared with none of the day case children ($\chi^2=5{\cdot}9$, $p<0{\cdot}025$).

As might be expected, the parents of children admitted as day cases were mostly able to stay with their children all the time that the children were on the ward (32 out of 35) compared with only a minority of the parents of the inpatient group (five out of 23) ($\chi^2=23{\cdot}6$, $p<0{\cdot}001$).

Parents were asked at one week after discharge what length of stay they would have preferred for their children. One third (seven out of 23) of the parents of the inpatient children would have preferred a shorter stay and none a longer stay. Parents of four of the 35 day case children would have preferred a longer stay and three an even shorter stay ($\chi^2=6{\cdot}9$, $p<0{\cdot}05$).

There were no extra demands for community care facilities in the day case group. This is being reported in detail elsewhere. No differences between the two groups were detected by the questionnaires in the remaining five points looked at—that is, in the degree of upset on admission to hospital, in the amount of postoperative pain, in the frequency of infection, or the difficulty with micturition after discharge home, and in the amount of upset during dressings of the wound.

Discussion

There have been many reports of psychological upset in children during and after admission to hospital; Fletcher has provided a comprehensive review.[3] However, relatively few randomised controlled trials have been carried out. The disturbance to the child has been found in two (non-randomised) studies to be less if the parents sleep in the hospital with their child.[6] [7] Many parents are unable to stay and sleep in the hospital, however, even if the opportunity is offered. The usual reason for this is responsibility for other children at home, but some parents are themselves afraid of the hospital environment and are reluctant to remain there any longer than is absolutely necessary.

A reduced length of hospital stay is another method of reducing separation of children from their parents. In the present study we attempted to assess any difference in upset between children admitted as day cases and children admitted for two nights by means of a randomised controlled trial using questionnaires. The questionnaires used appear to have been effective in detecting psychological effects in that the questions devised were able to detect significant differences between the two groups of children.

On the one hand, less upset might be expected in the shorter stay group because of a shorter exposure to the disturbing environment of the hospital; and on the other hand more disturbance might be expected in the shorter stay group if parental anxieties about care of the child discharged home soon after a general anaesthetic and surgical procedure were communicated to the child. In the event the shorter stay group was appreciably less affected by hospital admission. According to the parents' responses, inpatient children needed more attention on discharge home and were more likely to be still affected by their hospital stay three months later. The questions were designed to measure the child's behaviour or change in behaviour, and it is open to question whether the demonstration of a greater change in behaviour in the inpatient children is a valid method of showing a greater detrimental effect of hospital admission, however, this does seem the most compelling interpretation.

In view of the effect on the children staying in hospital for two nights, it is not surprising that one third of the parents of these children would have preferred a shorter stay in hospital. It is also worth noting that some of the parents of the children treated as day cases would also have preferred a shorter stay—the children were in hospital from 8 am to 5 pm—but further shortening of the period of postoperative observation is controversial.

Apart from minimising the effect on the child, another reason for keeping hospital stay to a minimum is the reduction in cost that results, although precise figures are difficult to give. Other possible arguments for shorter hospital stays are reductions in lengths of waiting lists and reduction in cross infection.

On all these grounds it seems that efforts should be made to reduce hospital stay as far as possible With regard to the psychological effect on the child, the point was brought home to us by several comments on the returned questionnaires of the longer stay children such as 'He's always saying "you left me on my own, in hospital and went away." '

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Fructosamine or glycated haemoglobin as a measure of diabetic control?

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SUMMARY Glycated haemoglobin A_1 (HbA_{1c}), fructosamine, and total serum proteins were measured in 30 normal and 61 diabetic children. The normal range for HbA_{1c} was 4·7–8·8% and for fructosamine was 0·98–1·88 mmol/l. These were similar to adult normal ranges and there were no significant age differences during childhood. There was a highly significant correlation between HbA_{1c} and fructosamine in the diabetic children but this was lost when only concentrations within the established normal ranges were considered. Adjustment of concentrations of fructosamine for total serum proteins made no difference to the results. Changes in HbA_{1c} and fructosamine were followed in three newly diagnosed patients and in one whose diabetes was getting worse. HbA_{1c} decayed with a half life of 28·7 days and fructosamine decayed with a half life of 16·5 days. Fructosamine concentrations were lower than expected in the patients who were improving and higher than expected in the patient who was deteriorating.

It is suggested that while fructosamine is not a direct substitute for HbA_{1c} it may be a useful adjunct in determining whether a patient is worsening or improving in the short term. A change from HbA_{1c} to fructosamine for routine assessment of diabetes while retaining HbA_{1c} on selected occasions would result in some cost savings while retaining the advantages of having both assays available.

In recent years measurement of glycated haemoglobin A_1 (HbA_{1c}) has been widely introduced as a measure of medium term control of diabetes and is used by many diabetologists as the yardstick by which diabetic control is judged. However it is subject to a number of disadvantages. It requires incubation for several hours to remove the unstable intermediate Schiff base, it is quite a time consuming assay to perform and, by comparison with the measurement of other ketoamines, relatively expensive. More recently, a method has been described for the measurement of glycated serum proteins, known as fructosamine, which is based on a colorimetric determination utilising the reducing properties of fructosamine at high pH.[1] It has the advantage that it is rapid, inexpensive, and can be automated, thus reducing the amount of laboratory time required for the assay. We have estimated that each HbA_{1c} assay costs roughly 50p to perform while estimations of fructosamine cost only a few pence if the reagents are made up in the laboratory or about 25p if the reagents are obtained in kit form.

We have used both of these assays to establish a normal range for both HbA_{1c} and fructosamine in children and applied them to the study of diabetic children to determine whether fructosamine might be a suitable alternative or a useful adjunct to HbA_{1c} in their routine management.

Methods

HbA_{1c} was measured using an immobilised boronic acid microcolumn technique after overnight incubation to remove the unstable fraction.[2] In our laboratory this assay has a coefficient of variation of 4% when HbA_{1c} equals 12% and 8% when it equals 5%.

Fructosamine was measured as previously described.[1] Venous plasma was added to carbonate buffer at pH 10·8 containing nitroblue tetrazolium 0·25 mmol/l. The absorbance at 530 nm was measured 10 and 15 minutes after mixing and compared with a secondary serum standard which itself had been calibrated against 1-deoxy, 1-morpholino fructose in albumin solution (40 g/l) that had been treated in identical fashion. The whole assay was carried out at 37°C. Analysis was made using a Centrifichem centrifugal analyser. This is able to handle 24 samples simultaneously and each batch takes about 20 minutes to perform.

Patients

A normal range of HbA_{1c} and fructosamine concentrations in children was established for our laboratory by measuring both variables on samples taken at the time of routine venepuncture in 30 children who were admitted to hospital either for routine surgery or for medical reasons unrelated to abnormalities of blood glucose control. All of these patients had a blood glucose within the normal range at the time of sampling. Verbal consent was obtained from the parents at the time and the study received ethical committee approval. The children were initially divided into three age groups: 0–5 years, 5–10 years, and 10–15 years to assess any age related changes in either variable. Differences were sought using non-parametric statistical methods (Mann-Witney U test).

HbA_{1c}, fructosamine and total protein were measured on the same samples taken from patients attending the children's diabetic clinic between January 1985 and June 1986. The samples were obtained either by venepuncture or by finger prick and stored in fluoride oxalate tubes until sent to the laboratory. A fructosamine:protein ratio was derived by dividing the fructosamine concentration (in μmol/l) by the total protein concentration (in g/l). HbA_{1c} was then plotted against both fructosamine and fructosamine:protein ratio and the appropriate linear regressions and 95% confidence limits fitted by the method of least squares.

Both variables were measured at diagnosis and at frequent intervals for up to 19 weeks in three patients who were newly diagnosed. In all three the diabetes was rapidly brought under control and the blood glucose returned to near control values. The concentration of fructosamine at equilibrium (C) is determined by the 'black box' relationship[3] and is dependent upon the rate of glycation (ΔG) and the half life ($t\frac{1}{2}$) of the proteins which are glycated according to the formula:

$$C=\Delta G \times t\tfrac{1}{2}/\ln 2$$

Preliminary data in our laboratory suggest that the rate of synthesis of fructosamine in vitro is directly proportional to the concentration of glucose in serum over a wide range. If the same is true in vivo,[4] the concentration of fructosamine at any one time is directly proportional to the integrated blood glucose concentration during a period determined by the half life of the glycated proteins, assuming that the concentration of those proteins remains constant, which was shown in the case of our patients.

From the 'black box' relationship it can be seen that it is only possible to estimate the half lives of HbA_{1c} and fructosamine if their rates of synthesis are known. These can only be calculated precisely if the mean blood glucose concentration over the period studied is recorded. As this was not possible, for the purposes of these calculations, the mean values of the normal range of HbA_{1c} and fructosamine were then subtracted from the appropriate observed value to eliminate the effect of de novo synthesis and the half life of each estimated from these derived values.

The observed values of HbA_{1c} and fructosamine in these three patients, together with those of a fourth patient whose condition had been improving but then progressively worsened over several weeks (HbA_{1c} concentration rising from 13·3% to 20%), were plotted against one another. Comparison was made with the regression line previously derived from the combined data of all the patients in the clinic in order to determine any differences between improving and worsening diabetes in the observed as against expected concentrations of fructosamine for a given concentration of HbA_{1c}.

Results

Table 1 shows the means and standard deviations of HbA_{1c} and fructosamine concentrations in the 30 normal children divided into the three age groups. There were no significant differences between the values in the groups so they were all combined. Mean (SD) HbA_{1c} concentration was 6·30 (1·08)% and fructosamine concentration was 1·33 (0·23) mmol/l with observed normal ranges (in the 30 children studied) of 4·7–8·8% and 0·98–1·88 mmol/l. The upper limits of normal values were therefore taken as 9% and 1·9 mmol/l, respectively. There was no significant relation between HbA_{1c} and fructosamine in these subjects.

Individual concentrations of HbA_{1c} and fructosamine in 129 samples from 61 diabetic children are shown in fig 1. A highly significant relation ($p<0·001$, $r=0·69$) was indicated and the linear regression and 95% confidence limits are shown When data points corresponding to values of HbA_{1c}

Table 1 *Mean (SD) glycated haemoglobin A_1 and fructosamine concentrations in 30 normal children*

Age	*Glycated haemoglobin (%)*	*Fructosamine (mmol/l)*
0–5	6·0 (1·0)	1·3 (0·2)
5–10	7·0 (0·8)	1·3 (0·2)
10–15	6·2 (1·1)	1·5 (0·3)
Mean (SD)	6·3 (1·1)	1·3 (0·2)

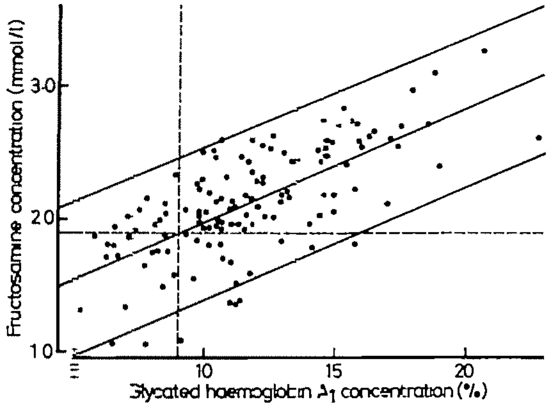

Fig 1 Relation between glycated haemoglobin A_1 and fructosamine in 129 samples from 61 diabetic children. The linear regression and 95% confidence limits are shown The interrupted lines represent the upper limits of normal of the two assays. For glycated haemoglobin A_1 $\leq$9·0% r=0·34 p=NS.

outside the normal range were excluded, however, the relation significance could not be shown. When HbA_{1c} was plotted against the fructosamine:protein ratio rather than fructosamine almost identical results were obtained. There was very little variation in total protein between patients (mean (SD) 65·25 (4·36) g/l) and the similar relation (r=0·68, $p<0·001$) suggested that the fructosamine:protein ratio calculation confirmed no advantages over fructosamine in these patients and has therefore not been considered further.

The changes in HbA_{1c} and fructosamine with time from diagnosis in the three patients who were newly diagnosed and being brought under control as shown in figs 2 and 3. In all three patients fructosamine concentration had returned to within the normal range by 40 days. In contrast the HbA_{1c} concentration was still raised at this time in all three and in one case was still raised at 80 days. Half life values of HbA_{1c} and fructosamine were calculated as described above for all three patients; both showed an apparent single half life of decay and the results are shown in table 2. In all cases the half life of fructosamine was shorter than that of HbA_{1c} (mean 16·5 v 28·7 days). Also shown in figs 2 and 3 are the concentrations of HbA_{1c} and fructosamine plotted against time in the one patient whose condition worsened.

Fig 4 shows the HbA_{1c} and fructosamine concentrations in all four patients plotted against each other and compared with the observed regression line. In all three newly diagnosed patients the fructosamine concentrations were lower than ex-

Table 2 *Half life of glycated haemoglobin A_1 and fructosamine in three newly diagnosed patients*

Patient No	*Sex*	*Days from diagnosis*	*Half life (days)*	
			Glycated haemoglobin A_1	*Fructosamine*
1	F	82	34·5	18·2
2	F	99	22·3	13·6
3	F	133	29·3	17·6
Mean			28·7	16·5

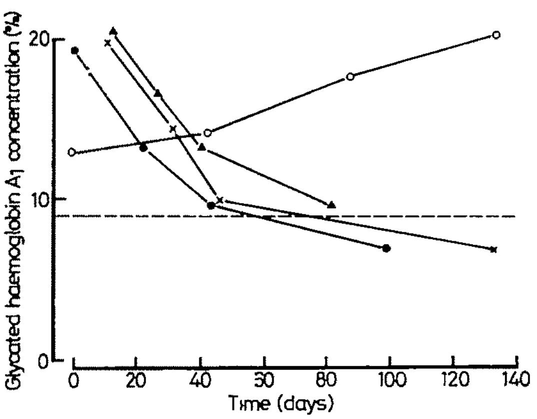

Fig 2 *Changes in glycated haemoglobin A_1 in three newly diagnosed diabetics (●——●; ×——×; ▲——▲) who were rapidly brought under control and one other patient (○——○) whose diabetes worsened The interrupted line represents the upper limit of normal*

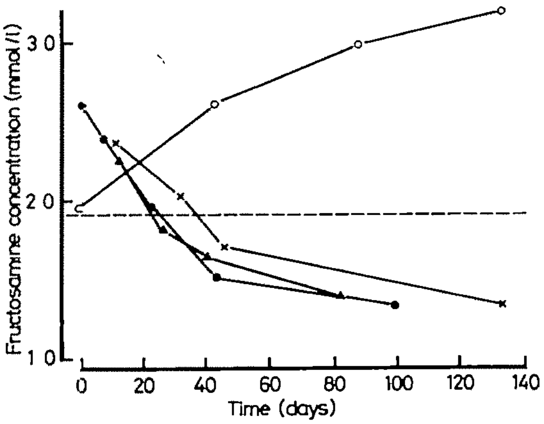

Fig 3 *Changes in fructosamine in three newly diagnosed diabetics (●——●, ×——×, ▲——▲) who were rapidly brought under control and one other patient (○——○) whose diabetes worsened. The interrupted line represents the upper limit of normal.*

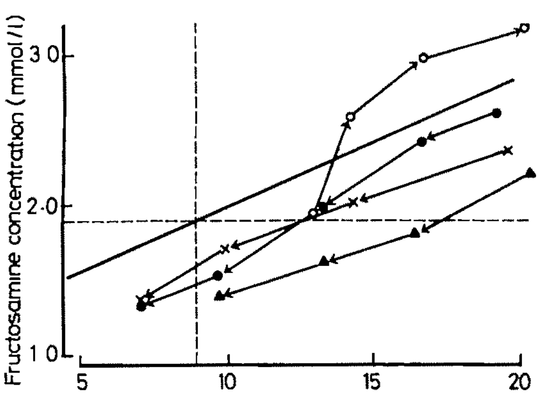

Fig 4 *Relation between glycated haemoglobin A_1 and fructosamine in four patients compared with the regression statistic The three newly diagnosed patients. (●——●; ×——×, ▲——▲) were rapidly brought under control, in the other patient (○——○) the diabetes worsened. Arrows indicate direction of progress*

pected since the points fell below the regression line. Conversely all the points derived from the period of deterioration in the fourth patient lay above the regression line indicating a concentration of fructosamine that was higher than expected.

Discussion

Poor diabetic control leads to an increased incidence of long term complications, particularly retinopathy and nephropathy,[5–7] and maintenance of good control can help to delay their onset. Objective methods of assessing diabetic control have been increasingly used in the past decade to help achieve the aim of near normoglycaemia. HbA_{1c} has been the mainstay of these methods but recently fructosamine has been introduced and is now measured routinely in some clinics including our own. The results of these studies show that the ranges of HbA_{1c} and fructosamine in normal children are very similar to those of normal adults and no age related differences were shown.

Fructosamine concentration measured as described here has been shown to reflect mainly the concentration of high molecular mass ketoamines or glycosyl proteins[2] with little or no interference by other physiologically important reducing substances under the conditions used. It is therefore a useful indicator of glycaemic state in the period before its measurement.

The method of estimating the half lives of HbA_{1c} and fructosamine assumed that the blood glucose in the diabetic children promptly returned to a mean normal value at the start of treatment and was maintained so thereafter. It also assumed that a mean normal blood glucose would yield mean normal HbA_{1c} and fructosamine was unaffected by the diabetic state. While the latter two assumptions are reasonable, clearly the first is not and the effect of this is to give values of the half lives that are slightly longer than the true one. Nevertheless, it is valid to compare the two half lives as, during the period studied, both were subject to the same influences of blood glucose fluctuations.

We have shown that the half life of HbA_{1c} is about four weeks and confirmed the finding of others that the half life of fructosamine is substantially shorter at two and half weeks.[8 9] It is, therefore not surprising that the correlation between HbA_{1c} and fructosamine was only 0·69 and that this disappeared when only values within the normal range were included, although it has been claimed that the different half lives of the substances is not the only contribution to this finding.[10] Fructosamine is therefore not a direct substitute for HbA_{1c} and the advantages and disadvantages of each assay must be considered when deciding whether it might be a suitable alternative, as has been previously suggested.[11 12] The introduction of fructosamine in addition to HbA_{1c} would inevitably increase the overall costs of assessing diabetic control (by about 10–15% if the reagents are made up in the laboratory) and cannot be reasonably justified as a routine measure. Conversely, a complete change to fructosamine as an alternative to HbA_{1c} would only lead to small annual savings (in a paediatric clinic) and is difficult to justify on clinical grounds at least until more widespread experience has been gained with the assay. The relatively short half life of fructosamine leads to a rapid improvement in its concentrations after a short period of good control and may give a false sense of security regarding longer term control that measurements of HbA_{1c} might indentify unless more frequent fructosamine estimations are made. In addition, conditions associated with reduced plasma proteins or increased rates of protein turnover such as pregnancy or nephrotic syndrome would be expected to give falsely low fructosamine concentrations.

Perhaps the best policy is to use fructosamine instead of HbA_{1c} for most routine purposes while retaining occasional HbA_{1c} estimations (for example, once a year as part of an 'annual check') in addition. Furthermore, as we have shown that as expected, fructosamine concentrations are lower than predicted by HbA_{1c} when patients are improving and vice versa, it may be possible to use the two parameters together, under certain circumstances, to determine whether a patient is improving or worsening in the short term. Fructosamine may be a useful adjunct to HbA_1 in this respect. Such a policy would still reduce the overall costs of assessing diabetic control while retaining the flexibility of having both assays available. Further studies are needed to test this hypothesis.

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Isolated pulmonary histiocytosis

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SUMMARY Pulmonary disease in the 'histiocytosis syndromes' is not uncommon. Isolated pulmonary histiocytosis, however, is rarely diagnosed. We describe three patients with this condition, with ages ranging from 3 weeks to 9½ years, in whom there was no evidence of disease in any other organ. Their presentation, treatment, and clinical progress over three years of follow up are discussed.

Pulmonary histiocytosis most commonly occurs as part of multisystem disease by histiocytosis X. Disease limited to the lung is recognised as a cause of interstitial lung disease in adults[1] but has not been extensively reported in children.

We report here three cases of isolated pulmonary histiocytosis and describe their clinical course in the three years since diagnosis.

Case reports

Case 1. A 2 month old boy presented with a clinically diagnosed bronchopneumonia. Persistent cough and breathlessness were accompanied by poor feeding, vomiting, and weight loss. On examination he was tachypnoeic, not cyanosed, but crepitations were audible over both lung fields. A chest radiograph showed soft hazy infiltrative changes in both lungs, which were more noticeable on the left (fig 1). He was treated with antibiotics and chest physiotherapy with some resolution in his symptoms. At 4 months of age he had a further exacerbation of breathlessness that was accompanied by wheezing and cyanosis. A further chest radiograph showed asymmetrical fine reticular infiltration of the left lung. Isotope lung scanning showed normal perfusion, but diminished ventilation in the right lung. Histological examination of a specimen from an open lung biopsy of the left lower lobe showed diffuse proliferation of histiocytes between alveoli and around terminal bronchioles; this was compatible with a diagnosis of pulmonary histiocytosis X.

After a course of treatment with vinblastine, prednisolone, and etoposide (VP16) there was a definite improvement. Steroids were continued until the age of 15 months. At 3 years of age he remains free of symptoms and is on no treatment. Clinically he has some chest overinflation with sternal prominence, and his height and weight are following the 50th and 10th centiles, respectively. The most recent chest radiograph showed reticular shadowing in both lung fields in the upper and mid zones. Histiocytosis has not developed at any other organ site.

Case 2. A 3 week old girl first presented with a two day history of cough, breathlessness, and slow feeding. She was feverish and had signs of respiratory distress with widespread crepitations and wheezes over both lungs. The rest of the examination was normal. A chest radiograph showed patchy shadowing in the right upper zone and antibiotics

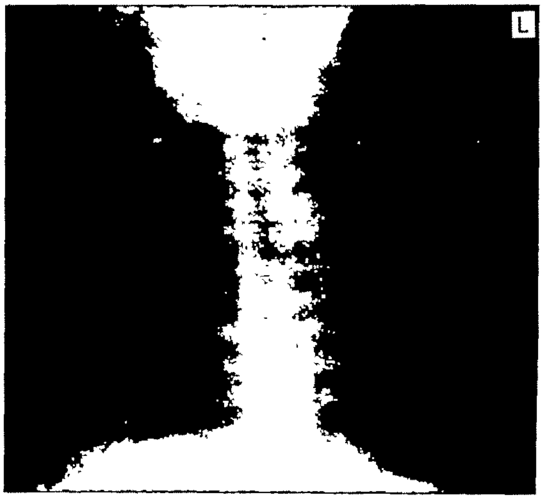

Fig 1 *Chest radiograph of case 1, aged 2 months at the time of presentation, showing soft hazy infiltrative changes, most noticeable in the left lung.*

were prescribed for what was thought to be bronchopneumonia. Her condition improved but she was readmitted two weeks later with a similar illness and this was followed by a further six episodes warranting admissions during the first [illegible] months of life There was severe failure to thrive with an appreciable fall off in weight. Medication including inhaled β_2 agonist bronchodilators, anticholinergic agents, antibiotics, and corticosteroids failed to show any improvement in her condition Extensive investigations were performed; sweat chloride analysis and serum immunoglobulins gave normal results as did bronchography and a contrast oesophagogram. Serial chest radiographs showed widespread infiltrative changes and fine nodular shadows mainly in the upper and midzones of the left lung (fig 2). Isotope lung scanning showed mismatching with a greater diminution in ventilation than perfusion to these areas. At 1[illegible] months of age an open lung biopsy specimen showed infiltration of peribronchiolar and interalveolar walls by proliferating histiocytes. Full evaluation including bone marrow aspirate examination, plain radiograph skeletal survey, and isotope bone scan did not show evidence of histiocytosis at any other site. Treatment with prednisolone and vinblastine was given, but no improvement occurred until etoposide was substituted for vinblastine. There was then a noticeable improvement of respiratory symptoms and growth.

At 3 years 7 months of age, when clinically her symptoms were well controlled, a respiratory arrest occurred at home and the child was brought into hospital dead. At postmortem examination the findings showed pulmonary histiocytosis Both upper lobes contained small emphysematous cysts beneath the pleural surface and numerous small yellow nodules These nodules showed the histological features of histiocytosis X.

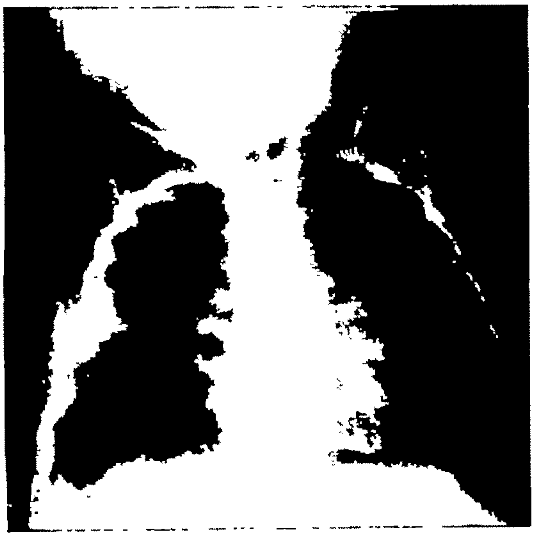

Fig 2 *Chest radiograph of case 2, showing widespread infiltrative changes and nodular shadows in the left lung.*

Case 3. A boy, aged 9½ years, was referred because he had had a recurrent cough for four months that had been unresponsive to inhaled β_2 agonist bronchodilator treatment. Physical examination was normal and initial chest radiograph showed only minimal perihilar streaking Symptoms persisted and after a further three months the radiological

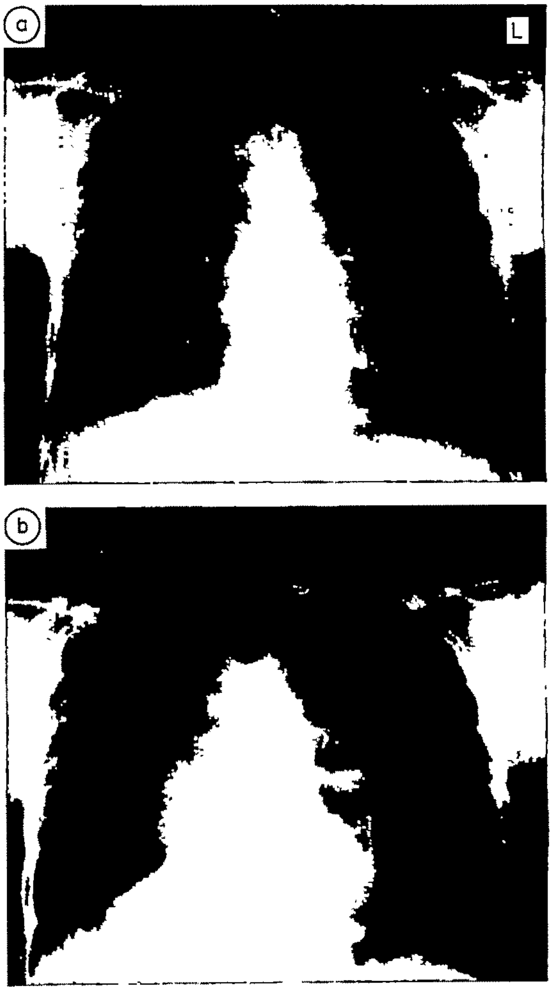

Fig 3 *Chest radiographs of case 3 (a) at presentation showing perihilar streaking and (b) three years later: this shows the progression to fibrotic changes with partial lobar collapse and granularity in the right midzone.*

features had progressed to extensive perihilar and paratracheal streaky infiltrative changes accompanied by loss of lung volume (fig 3a). On chest ausculation crepitations were present over both lungs, but there was no wheezing Peak expiratory flow rate was 67% predicted for height, and did not improve significantly after inhaled bronchodilators. Further pulmonary function tests showed a reduction in vital capacity (45% predicted), more so than functional residual capacity (78% predicted, measured by helium dilution). This reduction occurred at the expense of increased residual volume so that the ratio of residual volume to total lung capacity was increased (38%). The ratio of forced expiratory volume in one second to forced vital capacity was normal (85%). This reflects a restrictive defect with evidence of gas trapping. Isotope lung scanning showed patchy decreased ventilation to the left base but normal perfusion. As a consequence of this mismatching he was hypoxaemic at rest (PaO_2 7·9 kPa). An open lung biopsy specimen showed infiltration of peribronchiolar tissue and alveolar walls by histiocytes and plasma cells. He has remained well with minimal respiratory symptoms, and there is no disease in any other organ system in the three years since diagnosis. Despite absence of symptoms and physical signs his pulmonary histiocytosis has progressed radiologically with more noticeable perihilar streaking and fibrotic changes leading to partial right lower lobe collapse (fig 3b). There are no clinical or electrocardiographic signs of pulmonary hypertension.

Discussion

Histiocytosis limited to the lung as described in these three cases is a rare cause of interstitial lung disease in childhood. The entity, histiocytosis X, encompasses an overlapping group of disorders that share the common histological features of proliferation of atypical histiocytes, but each disorder has widely different patterns of organ disease and a variable prognosis ranging from excellent to lethal [2] The lungs are affected in 50% of children who have multisystem disease[3] but much of what is known about isolated lung histiocytosis is based on the experience in adult practice of a relatively benign, frequently self limiting cause of interstitial pneumonitis in the young or middle aged [1] Reports of 'primary pulmonary histiocytosis' in children[4] and adults[5] have included patients with histiocytosis disease at other organ sites outside the lung. To our knowledge there have been only three previous reports in children of lung histiocytosis X as the sole organ to be affected.[6-8]

Two of the children reported here presented early in infancy with failure to thrive and persistent breathlessness. Both infants had presentations suggestive of alternative diagnoses and their initial chest radiographs were not typical of interstitial lung disease Only later in the clinical course did nodular or reticular shadows become apparent, and these were accompanied by prominent perihilar streaking.

The usual radiographic features of primary pulmonary histiocytosis in adult patients are fine or coarse reticular or nodular infiltrates in the upper and midzones with notable sparing of the costophrenic angles.[9] If the disease progresses small cysts or bullae appear and eventually there is fibrosis and 'honeycombing'.[1] Hilar lymphadenopathy is unusual. The radiological features of primary pulmonary histiocytosis are not specific enough to make the diagnosis in adult practice, and our experience in children would support this. Investigations, other than lung biopsy, were not of diagnostic value but are necessary to exclude important alternative diagnoses. Pulmonary function testing in adults has shown variable patterns but the most consistent abnormality has been depression of diffusion capacity reflecting disease of the alveolar capillary vasculature.[1] Isotope ventilation/perfusion scanning in two of our patients gave considerably abnormal results though certainly not specifically diagnostic for histiocytosis. In general ventilation was more impaired than perfusion, and the areas affected were more extensive than shown radiologically. Isotope scanning of this type may be of value in serially following affected children as it is apparent that clinical symptoms, signs, and radiological appearances do not necessarily parallel one another. Gallium 67 isotope scanning has been unhelpful in adult patients.[10]

The histology of histiocytosis in the lung is not essentially different between primary pulmonary histiocytosis and the disseminated disease. The lungs contain yellow or grey nodules and subpleural cysts, which are predominantly in the upper lobes and vary in size from 1 mm to 1·5 cm. The nodules contain mainly atypical histiocytes (Langerhans cells) and eosinophils with few lymphocytes. This infiltrate is mainly peribronchiolar but is also present in the alveolar wall and around small vessels and capillaries. Langerhans cells are not normally present in the alveolar wall and rarely present in the bronchilar wall of the adult lung.[9] Electron microscopy of Langerhans cells shows characteristic cytoplasmic organelles (Birbeck granules). On disease progression affected areas are replaced by fibrous tissue leaving characteristic stellate shaped scars.

It is now thought that histiocytosis X is a non-malignant proliferative disorder of the Langerhans cell system, and that histiocytes share numerous morphological and biological features with macrophages. The Langerhans cell system can be regarded as a subpopulation of the mononuclear cell system and is closely allayed to T cell populations and the lymphocytic immune system.[11 12] Identification of Langerhan cells containing Birbeck granules can now be performed using the monoclonal antibody OKT6 and antibody to S100 protein.[4 13]

Such is the apparent rarity of isolated pulmonary histiocytosis in children that it is likely that only the most severe or fatal cases will be reported, therefore conclusions about clinical features, treatment response, and natural history must be viewed with caution. In our experience there is an initial phase of prominent respiratory symptoms (and growth failure in infants) but radiological features are not typically nodular or reticular until later. After a variable period the symptoms improve considerably but radiological signs of the disease do not show any resolution and may even show a progression.

The cause of death in case 2 at the age of 3 years 7 months is unexplained by postmortem findings. Despite extensive pulmonary disease with cyst formation she appeared to have been symptom free for some while We speculate that she suffered catastrophic pneumothoraces from rupture of a subpleural cyst; this is a complication of pulmonary histiocytosis occurring in up to 10% of adult cases.[5]

Unlike histiocytosis limited to other single organ sites where the prognosis is usually good, the prognosis for primary pulmonary histiocytosis in childhood is, at best, unpredictable. Based on current available information no strong recommendations can be made for the treatment of primary pulmonary histiocytosis, although a therapeutic trial of steroids in symptomatic patients is justified.

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The trisomy (5)(q31–qter) syndrome: study of a family with a t(5:14) translocation

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SUMMARY We report a child with multiple malformations caused by trisomy for the distal part of the long arm of chromosome No 5. A neonatal diagnosis of Down's syndrome had previously been made on the basis of clinical examination and the detection of an additional chromosome not unlike No 21. A subsequent clinical re-evaluation, with the cooperation of the parents who permitted further studies, led to the confirmation of the true diagnosis. The mother was the carrier of a balanced translocation between chromosome No 5 and No 14. The child had severe growth and psychomotor retardation and characteristic features: microcephaly, antimongoloid slant, epicanthus, low set ears, downturned mouth, and long upper lip. She was hypertonic and a congenital heart disease (atrial septal defect) was present. We have compared this case with others known to be trisomic for segment 5q31–qter.

Though increasing numbers of patients with small chromosomal duplications and deficiencies are being shown by improvements in G-banding resolution, compared with classical trisomics and major deletions, they remain small in total. There are also appreciable differences in frequency, presumably related to potential viability, between different duplications of even the same chromosomes. Thus in chromosome No 5 there are far more partial trisomies for 5p, a well recognised syndrome, compared with duplications of the long arm (5q). Less than 20 such cases have ever been discovered[1]; all except three represented trisomies for the terminal zone. We recently carried out a re-evaluation of a child who had been studied in the neonatal period and she proved to be mostly trisomic for the distal part of 5q (q31 to qter); this resulted from a balanced t(5:14) translocation in the mother. There are only seven cases from five families in the literature with the same duplication, all of them involved different translocation combinations from the case reported here.[2–6]

Case report

A girl, now aged 3 years, was the fourth child of the second marriage of an English mother and Gambian father. Her three male siblings were all clinically normal; the mother's fourth pregnancy ended in miscarriage. The first marriage resulted in three male children, all now adopted, the youngest of whom had congenital hydrocephalus and polydactyly.

The propositus was born at term after a normal pregnancy. Birth weight (2200 g), length (43 cm), and head circumference (32 cm) were all well below the third centile. Her facial appearance was unusual with a slight mongoloid slant of the palpebral fissures. She had a large umbilical hernia and there was a 2/6 ejection systolic murmur at the mid sternal edge. In the neonatal period she had had two episodes of cyanosis and breathlessness during feeds. Although the electrocardiogram was normal, the chest radiograph showed slight enlargement of the cardiac silhouette and mild pulmonary plethora. A subsequent cardiac assessment using echocardiography showed a secundum atrial septal defect. Treatment was commenced with digoxin and diuretics.

A chromosome analysis performed soon after birth indicated the presence of an extra chromosome similar in size and morphology to No 21 though the centromere region differed slightly. A pericentric inversion of chromosome No 9 was also present and blood samples from both parents were requested. These were not forthcoming and in view of the clinical and chromosome appearance a working diagnosis of Down's syndrome was made.

Further studies were not possible until she was aged 20 months when she was admitted to this hospital for investigation of severe failure to thrive and developmental delay. Her height, weight, and head circumference had remained well below and were falling further from the third centile (fig 1). Her facies were unusual but were basically lacking the more important positive stigmata of Down's syndrome, and the slope of the narrow palpebral fissures was now somewhat antimongoloid (fig 2). There was a right epicanthic fold, and the upper lip was long and associated with a slightly downturned mouth. The ears were small and low set. The hair was rather sparse and there was widespread excoriated eczema. The lower limbs were spastic with hypertonia and scissoring. A large umbilical hernia containing bowel was still present and the cardiac signs remained unchanged.

Investigations

Skull radiography showed premature fusion of the saggital and lambdoid sutures, but a computed tomogram was normal. The bone age was retarded (12 months). Audiology showed a bilateral mixed hearing deficit.

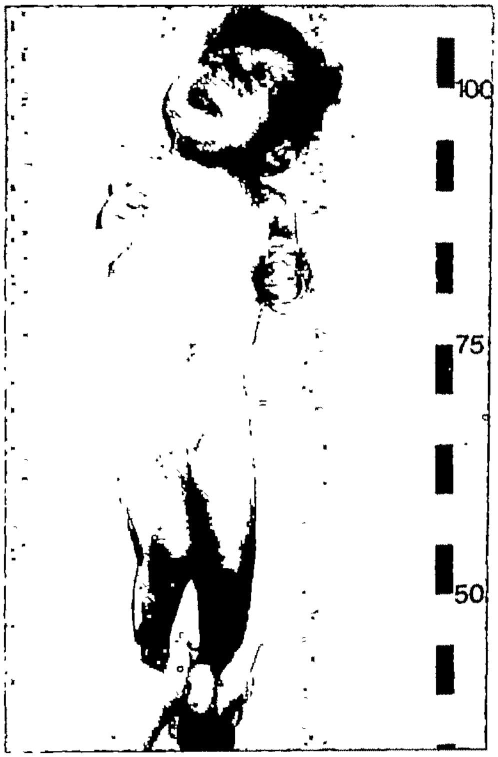

Fig 1 *Patient aged 21 months showing repaired umbilical hernia and poor growth.*

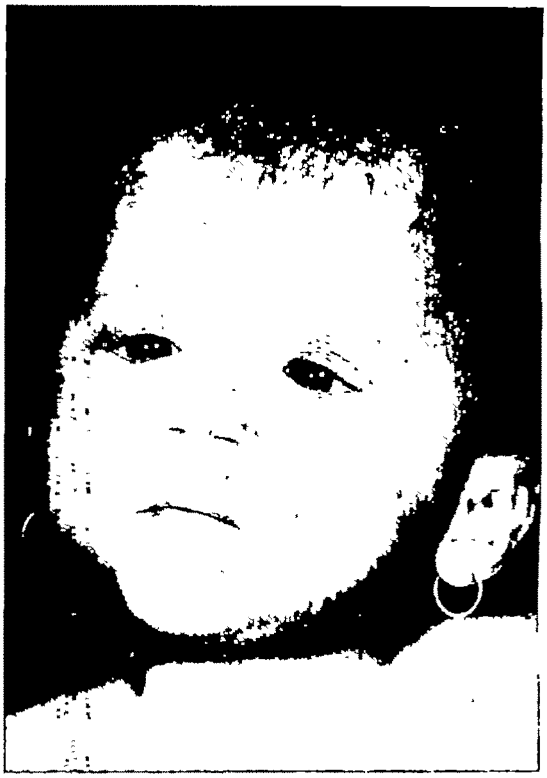

Fig 2 *Patient aged 21 months showing narrow palpebral fissures, dysmorphic facial appearance, and the sparse hair*

Results of biochemical and haematological investigations showed no evidence of malabsorption. Renal, adrenal, liver, and thyroid function tests gave normal results. Plasma and urine amino acid profiles were normal as were serum concentrations of trace metals including iron, zinc, and copper. A dermatoglyphic study showed an unusual combination of patterns consistent with a chromosome abnormality but not Down's syndrome. Six out of 10 digits had simple arch patterns and a distal t triradius was present on the right hand (fig 3) but not on the left. The D line exit was in the fourth interspace on the right, but the d triradius was absent on the left. There were no patterns on the thenar, hypothenar, and hallucal areas except for a small hypothenar loop on the right palm.

Cytogenetics

The opportunity was taken to study the patient further, and also to karyotype both parents. The centromere region of the additional acrocentric chromosome was different from the other G group chromosomes by virtue of a very small pale sub centromeric region in the long arm thus indicating that it was a translocation product. The distal segment of the long arm including the dense band, though similar to No 21, probably represented the terminal region of another autosome ending in a very pale telomere. The mother was found to have the same recombinant chromosome as her daughter, replacing a No 14, and this had resulted from a balanced translocation between No 14 and the terminal part of long arm No 5, the break points being respectively q11 and q31. (46,XX,t(5:14)(q31:q11)) (fig 4). The ovum at conception therefore contained a normal haploid set of 23 chromosomes together with the small recombinant chromosome. The father was the carrier of the No 9 with the pericentric inversion (46,XY, per.inv. 9).

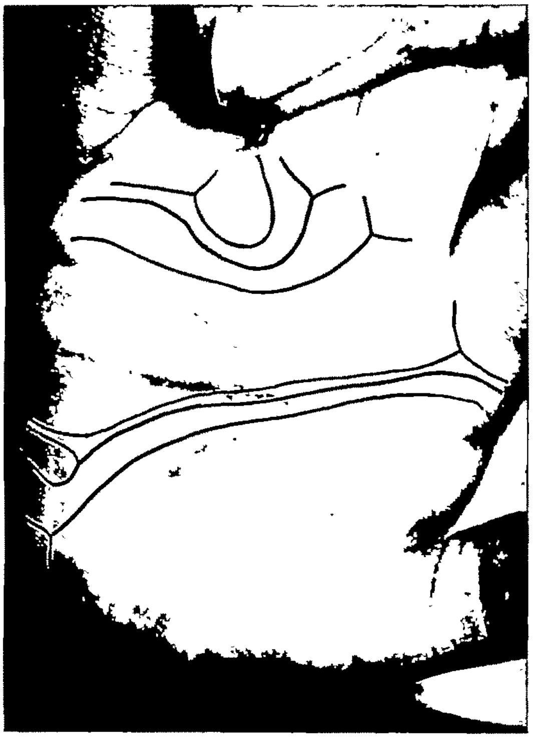

Fig 3 *Palmar creases and dermatoglyphic patterns (right hand)*

The propositus therefore resulted from a 3:1 segregation from the chain quadrivalent formed at pachytene in maternal meiosis. She is trisomic for the centromere region of No 14 and the segment q31 to qter of chromosome No 5. The three male siblings were all proved to be carriers of the same balanced translocation. It has not been possible to karyotype the three half siblings of the first marriage.

Progress and management

Her eczema responded dramatically to a diet free of milk and eggs. Treatment with digoxin and diuretic was continued and the umbilical hernia was repaired surgically. By the age of 25 months her speech was limited to short monosyllabic babble and there was moderate to severe hearing loss. Her Griffiths's scale performance was rated as 'general' 2 months, 'hand/eye coordination' 6 months, and 'social' 7 months.

A year later (aged 3 years 1 month) she was sitting unaided, walking with gaiters, and able to roll over. She could say two words and was finger feeding. However, she remained clearly microcephalic and dysmorphic in appearance with hypertonia.

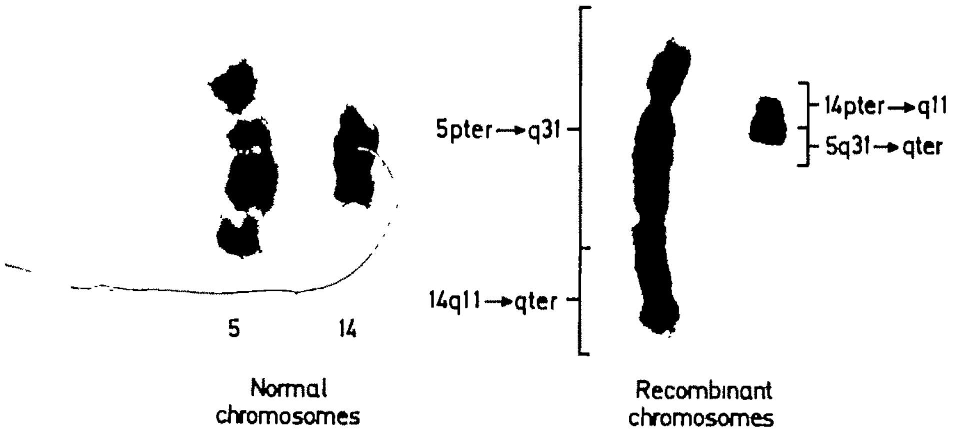

Fig 4 *Partial karyotype of mother showing a reciprocal interchange between chromosome Nos 5 and 14 with the break points as indicated (×10 000). Her daughter therefore received from her the small recombinant chromosome additional to a normal haploid set.*

Discussion

Though this child had a superficial resemblance to a child with Down's syndrome in the newborn period, detailed appraisal of her clinical features during her second and third years of life have established firm similarities with other patients having a proven duplication of the terminal region from band 31 of the long arm of chromosome No 5. The main malformations of a total of eight cases, including this case, are reviewed in the table.[2-6] In the series there is a predominance of females (seven female:one male). The average maternal age was not increased as all the cases resulted from familial translocations. All were of low birth weight with evidence of intrauterine growth retardation and growth that continued to fall away from below the third centile. Severe psychomotor retardation with deafness was soon apparent. Recorded cases are microcephalic with distinctive facies including antimongoloid slant of narrow palpebral fissures. Most have epicanthus and hypertelorism; strabismus may be present. The mouth is somewhat small and downturned with a rather long upper lip. The ears are usually low set and often large. There may be minor digital anomalies and there is a high frequency of cardiac malformation The child described here therefore represents a typical example of the syndrome. Some variation in the clinical appearance is to be expected, however, in view of the different chromosomes involved with No 5 in the rearrangements The age at the time of reporting in the previous cases varied from the newborn to 4 years and all were alive at the time.[2-6]

The results of chromosome segregation in this family will lead to normal and balanced carriers from regular alternate segregation in maternal meiosis, but grossly unbalanced and potentially non-viable zygotes will result from adjacent segregation because the size of the duplication and deficiency anomalies are so large. A 3:1 segregation of the normal No 5 and No 14 chromosomes with the small recombinant chromosome, however, represents only a small duplication and is presumably viable. Complete trisomics for Nos 5 and 14 from other 3:1 segregations are again not viable. On this basis it is likely that the defective half brother has the same chromosome imbalance as the propositus. Though clearly indicated, prenatal screening of future pregnancies in this family is unlikely as the mother is against termination of pregnancy under any circumstances.

This study indicates the importance of persistence in follow up in both the clinics and the laboratory despite initial lack of cooperation on the part of the parents. Only when samples from the parents were forthcoming, coupled with a re-evaluation of the child's karyotype and clinical signs including dermatoglyphics, could a definitive diagnosis be made

We are grateful to Mrs Karen Spencer for secretarial help

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Table *Clinical features of trisomy 5(q31–qter) in reported cases*

	Ferguson-Smith et al (1973)[2]	*Osztovics and Kiss (1975)*[3]		*Watanabe et al (1977)*[4]	*Jones et al (1979)*[5]	*Rodewald et al (1980)*[6]		*Present case*
		Case 1	*Case 2*			*Case 1*	*Case 2*	
Familial translocation	t(2:5)	t(2 5)		t(5 13)	t(5 9)	t(5 11)		t(5 14)
Growth retardation	+	−	+		+	+	+	+
Psychomotor retardation	+	−	+			+	+	+
Microcephaly	+	−	+	+	+	+	+	+
Antimongoloid slant	+					+		+
Epicanthus		−	+	+			+	+
Hypertelorism	+	−				+		
Strabismus		−	+			+		
Long upper lip		−			+			+
Downturned mouth						+		+
Micrognathia					+	+	+	
Low set ears (large)	+	−	+			+	+	(+)small)
Cardiac malformation			+	+	+			+

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Short reports

Liver failure and Epstein-Barr virus infection

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SUMMARY A 5 year old boy developed liver failure secondary to infection with Epstein-Barr virus. He was subsequently shown to have a partial C4 complement deficiency. The importance of considering Epstein-Barr virus as a cause of fulminant hepatic failure and the need to assess immune state in such an event is emphasised.

Case report

A 5 year old boy was referred because of increasing jaundice and confusion. He had been unwell for four days, initially he was just listless but he subsequently lost his appetite and started vomiting. On the morning of referral he was vomiting profusely and complained of abdominal pain, by the afternoon he was delirious and jaundiced There was nothing of note in his medical or family history. He had had no contact with hepatitis but had been on a school trip to a farm one week earlier. He had received no blood transfusions nor had he taken any drugs recently. On arrival at hospital he was drowsy and responded only to painful stimuli (grade IV coma). He was restless and had bite marks on his arms (self-inflicted). His pupils were dilated but reacted to light; his fundi were normal He had generalised hyper-reflexia and extensor plantar responses. He was deeply jaundiced with hepatic fetor, he was also dehydrated and had a blood pressure of 125/75 mm Hg and a temperature of 36·9°C. Neither his liver nor his spleen were palpable. He had no lymphadenopathy and his tonsils were normal.

The results of investigations were as follows: prothrombin ratio 5·2; thrombin time 18 seconds (control 14 seconds); kaolin cephalin clotting time 43 seconds (control 42 seconds), bilirubin concentration 594 μmol/l (direct bilirubin 301 μmol/l); alanine aminotransferase activity 5560 IU/l; alkaline phosphatase activity 310 KAU/l. Blood glucose was 4·3 mmol/l and plasma proteins were normal His haemoglobin was 109 g/l, white cell count $32·6\times10^9$/l, (83% neutrophils, 13% lymphocytes), platelets 294×10^9/l, reticulocytes 7·8%; the blood film was normal and a direct Coombs test gave a negative result.

His serum sodium concentration was 136 mmol/l, potassium 5·3 mmol/l, bicarbonate 17 mmol/l, urea 11·7 mmol/l, and creatinine 183 μmol/l Microscopy of the urine showed the presence of red cells and red cell casts and urinalysis gave a positive result for protein (++), blood (++++), and bilirubin (a large amount); the urobilinogen was normal.

A Paul-Bunnell test, Monospot test, and test for serum antibodies to Epstein-Barr virus all gave positive results (table) Serum C3 concentration was 0·86 g/l (normal range 0·55–1·20), C4 0·14 g/l (normal range 0·2–0·5), and C4 functional activity was 50% of normal as assessed by haemolytic assay.

The following investigations gave normal results: lumbar puncture; blood and urine culture; hepatitis B surface and core antigen tests; antibody titres to hepatitis A, cytomegalovirus and leptospira; analysis of immunoglobulins; and ultrasound examination of the liver and spleen.

He was managed on the intensive care unit. His fluids were restricted to 1000 ml/m^2/day of 10% glucose. He received fresh frozen plasma to improve

Table *Results of tests for serum antibodies to Epstein-Barr virus*

	At presentation	*Time after presentation*			
		2 Months	*4 Months*	*9 Months*	*12 Months*
IgM to Epstein-Barr viral capsid antigen	+	−			
IgG to Epstein-Barr viral capsid antigen	+	+			
IgM to Epstein-Barr virus nuclear antigen	−	−	−	+ weak	+ weak

his prothrombin ratio, vitamin K_1, cimetidine, lactulose, and oral neomycin. Ampicillin was started to cover the possibility of leptospirosis before the result of the Monospot test was known. Interestingly, he did not develop an 'ampicillin rash'.

For 24 hours he was in grade IV hepatic coma and received intravenous mannitol when his pupils became unreactive to light. He then improved rapidly with decreasing jaundice and an improved level of consciousness. Four days after presentation he was fully conscious and his serum bilirubin was 175 μmol/l, prothrombin ratio 1·4, and alanine aminotransferase 1400 IU/l. After two weeks his serum bilirubin was 29 μmol/l. His alanine aminotransferase was 39 IU/l after five weeks. One year after presentation he remains entirely well, but his C4 concentration and functional activity remain low.

Discussion

This 5 year old boy presented with a rapid onset of hepatic failure with evidence of glomerulonephritis shown by the presence of red cell casts in the urine. This was shown to be secondary to infection by Epstein-Barr virus as evidenced by a positive Monospot test and the presence of IgM and IgG antibodies to the viral capsid antigen. Other causes of liver failure were excluded. There were no clinical features to suggest infectious mononucleosis and he did not have an atypical lymphocytosis. He has a complement C4 deficiency that may account for the severity of his illness.

Numerous complications have been reported in association with infectious mononucleosis but severe jaundice with liver failure is very rare. Although raised aminotransaminase activities are found in roughly 80% of patients with infectious mononucleosis, clinical jaundice occurs in 5% only.[1] There are only 12 reported cases of hepatic failure secondary to Epstein-Barr virus infection with only one survivor. The fatal cases are reviewed by White and Juel-Jensen.[1] The sole survivor was a 25 year old man who developed signs of hepatic coma 16 days after presentation with a maximum serum bilirubin concentration of 170 μmol/l.[2] He recovered after being in stage III coma for two days; his recovery was attributed to the use of high dose steroids. All but one of the reported cases had typical clinical features of infectious mononucleosis. It is well known, however, that primary infection with Epstein-Barr virus often occurs in children without symptoms or typical clinical features.

It has been suggested previously that failure to develop atypical mononuclear cells during Epstein-Barr virus infection may represent a defect in cell mediated immunity.[3] There have been several reports of cases of fatal infectious mononucleosis where an immune defect has been identified, the most well known being those individuals with the X linked recessive lymphoproliferative syndrome (Duncan's disease). A severe illness consequent to Epstein-Barr virus infection in an individual with a complement deficiency, however, has not previously been reported. Individuals who are deficient in C4 may have an impaired immune response to viral antigen that could account for the severity of the illness experienced by this child.[4]

It is of concern that individuals with C4 deficiency have been reported to develop systemic lupus-like illness in later life[5] but at present the child reported here is well with no apparent sequelae from the liver failure or Epstein-Barr virus infection.

It seems remarkable that he survived considering the severity and rapid progression of his illness. It is felt that only 15–25% of children will survive grade IV hepatic coma.[6]

We report this case in order to indicate the importance of considering Epstein-Barr virus as a cause of hepatic failure and the need to assess immune state if this is the case.

We would like to thank Dr Gooi for his advice on the immunology and Dr JT Brocklebank for permission to report this case.

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Cranial diabetes insipidus in early infancy

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SUMMARY We report an infant who developed cranial diabetes insipidus after septicaemic shock. This condition should be considered in any child who suffers an acute collapse and it may be more common in the high risk neonate than has previously been recognised.

The aetiology of cranial diabetes insipidus in children has been well documented,[1] but the incidence in early infancy is unknown. This report concerns an infant who developed permanent diabetes insipidus after a hypotensive episode associated with meningococcal septicaemia.

Case report

A boy, birth weight 2500 g, was born at term after a normal pregnancy. There were no perinatal problems and a routine ultrasound examination of the head gave a normal result before discharge at 6 days The infant remained well until 6 weeks of age when he was readmitted to hospital after a sudden collapse. He was hypotensive and shocked and had a respiratory arrest soon after admission A lumbar puncture gave normal results but meningococcus type C was subsequently isolated from blood cultures. He was treated with ceftazidime to which the organism was sensitive but he remained unwell and had convulsions. A cranial ultrasound examination three days after admission gave a normal result. After a transient improvement he became lethargic and began to vomit. The cranial ultrasound examination now showed dilatation of the ventricles.

Fluid intake had been restricted during this period and the serum sodium concentration rose to 153 mmol/l. This increased further to 164 mmol/l despite an adequate fluid intake and it was noted that he was passing large volumes of urine in excess of 30 ml/hour with a specific gravity fixed at 1·000. Plasma and urine osmolalities were 337 and 66 mosmol/l, respectively and a diagnosis of diabetes insipidus was made. When the infant was rehydrated intravenously his condition improved. A further lumbar puncture gave a normal result and a cranial scan on computed tomography showed dilated ventricles which, in the absence of an increase in head circumference, suggested cerebral atrophy. A limited investigation of anterior pituitary function showed normal thyroid function and a normal random growth hormone concentration (23·7 mU/l); however, plasma cortisol concentrations were persistently low (<40 nmol/l). He was successfully treated with hydrocortisone 10 mg and intranasal desmopressin, 0·5–1 μg/day. Plasma and urine osmolality and serum sodium returned to normal after three days. He has poor head growth and at 10 months of age he has appreciable developmental delay

Discussion

Diabetes insipidus is rarely recognised in the neonatal period even though intracranial events such as hypoxic-ischaemic encephalopathy and intraventricular haemorrhage occur commonly at this time. Cranial diabetes insipidus, either permanent or transient, has been reported after intraventricular haemorrhage,[2] [3] listeria sepsis with disseminated intravascular coagulopathy,[4] and streptococcal meningitis.[5] This is the first report of permanent cranial diabetes insipidus developing in an infant after a hypoxic and hypotensive episode related to meningococcal septicaemia without meningitis. In addition the absence of a stress related increase in cortisol concentrations suggested deficiency of adrenocorticotrophic hormone. Hypotensive shock had presumably caused a reduction in cerebral blood flow sufficient to adversely affect hypothalamic-pituitary function. Similar aetiological factors have been invoked in isolated growth hormone deficiency.[6]

Fluid restriction is recommended whenever there is a risk of cerebral oedema formation. This treatment regimen, however, may obscure the signs of diabetes insipidus unless fluid balance and osmolality are carefully monitored. It is possible that a proportion of cases of 'idiopathic' cranial diabetes insipidus may be due to problems unrecognised during the newborn period. The condition, especially in a transient form, should be considered as an important sequela of collapse in sick infants and in neonates who suffer intraventricular haemorrhage or hypoxic-ischaemic encephalopathy.

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Atopic eczema and preterm birth

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SUMMARY In a group of 443 children with atopic eczema there was a significant lack of subjects born before 37 weeks' gestation. It is possible that preterm birth reduces the chances of the subsequent development of severe atopic disease.

It has been suggested that antigen exposure in the first weeks of life may sensitise the immunologically immature infant, triggering the development of atopic disease [1] If this were true one might expect an increased incidence of atopic disease in subjects born preterm, and this has been examined in a group of children with atopic eczema.

Subjects and methods

Between January 1982 and August 1987, 445 children with atopic eczema were referred to the department of child health. Eighty were referred by paediatricians, 32 by dermatologists, 312 by general practitioners and 21 by other doctors. The gestational age at birth was recorded as part of a full history taken from the parents at the first visit. Three hundred and ninety two patients (88%) were from the North West Region, 30 (7%) were from the local health district of North Manchester. The rest came from other parts of England and Wales. The median year of birth of the patients was 1981/2 Information about the gestational age of children still alive who were born in 1981 and 1982, to women currently living in the North West Region, was obtained from the North West Regional Health Authority. In these two years there were 87 606 children born who are still alive, and information about gestational age was available in 81 038 (93%).

Results

Information about gestation was unavailable in two patients who were adopted. There were three twins. The gestational age was reported to be 37 weeks or over in 428 (97%) and less than 37 weeks in 15 (3%). The gestational ages of the latter group were 36 weeks in seven children, 35 weeks in four, 34 weeks in three, and 29 weeks in one. The mean (SD) age of onset of the eczema was 6·8 (11·2) months The social class distribution of the parents of the patients was I and II, 169 (38%); III, 170 (38%); and IV and V, 106 (24%). Fourteen patients were illegitimate, and the fathers of 38 (9%) were unemployed. Of the 81 038 children whose mothers were currently living in the region and where gestational age was known, 4803 (6%) were less than 37 weeks' gestation and 76 235 (94%) were of 37 weeks' gestation or more. The distribution of gestation of the patients was significantly different from that of these 'control' children, $\chi^2=4\cdot66$, p=0·03.

Discussion

In a group of 443 children with atopic eczema, there was an unexpected and significant lack of subjects born preterm. As in any hospital based study the patients were highly selected, mainly by severity and poor response to topical treatment, but also by social class. A further drawback is that information about gestation was obtained from parents rather than from maternity records. Nevertheless, although parents may have overestimated or underestimated gestational age these errors should cancel each other out, and there is no reason to suspect that parents of atopic children are especially prone to overestimate gestational age. There is a modest excess of low birthweight and preterm infants in the lower social classes,[2] and a small excess of patients in this series from the higher social classes but this social class effect is insufficient to account for the findings of this study.

The findings of this study are not consistent with the hypothesis that atopic disease is simply the result of sensitisation in genetically predisposed infants who are immunologically immature. It appears that preterm infants are, if anything, less likely to develop severe atopic eczema than those born at or after term. It is known that preterm infants, if compared with term infants, have a decreased production of specific antibodies to cows' milk proteins during the first six months of life.[3, 4] Furthermore, the immunological effects of antigens in the neonatal period may be related not only to the state of maturity of the lymphoid system but also to that of the neonatal digestive system. It has been shown that the absorption of antigenically intact protein in infants less than 33 weeks' gestation may be up to 100 fold greater than at term,[5] and it is possible that the absorption of large quantities of antigenic material leads to tolerance rather than sensitisation.[6]

There are other possible explanations for these observations, such as protection from preterm delivery in atopic subjects, a lack of atopic disease among twins, or some difference in the method of feeding preterm infants. These possibilities need to be examined in a prospective study to discover the incidence of atopic disease in preterm infants. Protection from severe atopic eczema in preterm infants, if confirmed, could provide important clues about the pathogenesis of atopic disease.

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Mycotic intracranial abscesses during induction treatment for acute lymphoblastic leukaemia

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SUMMARY A boy with newly diagnosed acute lymphoblastic leukaemia developed mycotic cerebral abcesses despite treatment with amphotericin. He survived this episode on combination antifungal treatment.

Case report

A 13 year old boy presented with a week's history of bruising and a white cell count of $19 \cdot 4 \times 10^9/l$ of which 39% were blasts. He was febrile at presentation, with no obvious site of infection, and was started on intravenous cefuroxime and tobramycin with oral nystatin (100 000 units four times a day). An indwelling Hickman line was inserted and UKALL X induction, which included prednisolone 40 mg/m^2 for 28 days, was commenced.

On the fifth day of treatment he developed glycosuria, with a blood glucose of 25 mmol/l, and required insulin. Antibiotics were discontinued from day five, as bacterial cultures were negative, but were restarted on day 11 as he again became febrile and was neutropenic. The only positive culture was Aspergillus species on a throat swab; chest radiography was normal. Intravenous amphotericin was started on day 17 because of persistent fever. On day 28 routine bone marrow confirmed he was in remission. The next day, however, confusional episodes were noted with no accompanying gross neurological signs. Electroencephalography showed an excess of slow waves over the entire cortex.

Psychological testing showed unaffected verbal functioning but he could not cope with non-verbal tasks even at the level of a 5 or 6 year old. He was unable to copy accurately a series of designs. External objects seemed, to him, to change size and shape. Simple judgments made on visuo-spatial information could no longer be made—for example, he could no longer tell the time. In addition, if instructed to perform a series of motor actions, he would repeat the initial action again and again, despite being able to repeat correctly the verbal instructions. Focal brain damage was suspected.

A computed tomogram showed ill defined lucencies posteriorly in both cerebral cortices and anteriorly in the right frontal lobe, with no ring enhancement. The diagnosis was unclear; haemorrhage, infarct, cerebral leukaemia were all considered. Over the next few days he gradually deteriorated and a repeat computed tomogram, performed on day 37, then showed ring enhancement (figure).

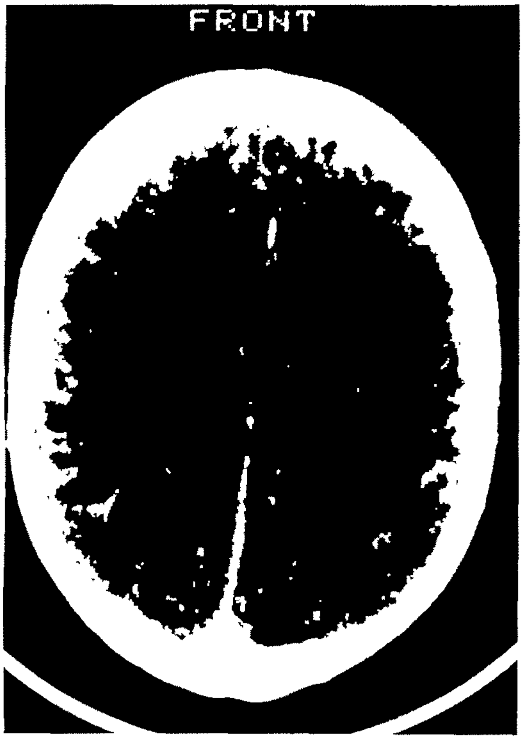

Figure *Computed tomogram with intravenous contrast showing the two occipito-parietal lesions*

A presumptive diagnosis of mycotic cerebral abscesses was made. No mycotic abscesses were shown in the liver or renal tracts. Blood and urine culture were negative for fungus. Candidial antibody testing, by counter immune electrophoresis, and antigen testing, using Cand-tec (Ramco Laboratories, Houston, Texas), were consistently negative before, during, and after his illness.

Oral flucytosine and oral itraconazole were commenced; the intravenous amphotericin was continued. Stereotactic aspiration of the abscesses was performed guided by computed tomography. Microscopy showed fungal hyphae and culture showed *Candida albicans* and anaerobic Streptococci. Benzylpenicillin was added, in high dose, to his antibiotic regime. Antifungals were given as follows: amphotericin 1 mg/kg (50 mg) alternate days for 10 weeks to a total dose of 1·75 g (started three weeks before the diagnosis of cerebral abscess); flucytosine 0·16 mg/kg (8 mg) daily for seven weeks; itraconazole 4 mg/kg (200 mg) daily for three weeks; benzylpenicillin was continued for a total of 12 weeks

This treatment was reasonably well tolerated, although renal potassium and magnesium loss required considerable intravenous supplementation. Creatinine clearance remained normal. There was no evidence of additional myelotoxicity. A repeat abscess aspiration one month after starting triple antifungal treatment was sterile on culture.

The recovery period was complicated by life threatening pneumonitis. An open lung biopsy specimen showed fine nodular infiltrates suggestive of varicella zoster. Fungi were not detected. He improved on intravenous acyclovir 10 mg/kg daily. Amphotericin and flucytosine were stopped seven weeks after the latter was started because of the development of hepatitis that was believed to be drug induced. This resolved satisfactorily.

A repeat psychological examination, 12 weeks after the diagnosis of cerebral abscesses, showed nearly complete recovery of all neurological processes. A computed tomogram at this time still showed some lucency in the occipitoparietal lobes and in the right frontal lobe but without ring enhancement. The importance of these findings remains uncertain. He managed a successful return to school.

It had been intended to give intensified leukaemia treatment on day 29, according to protocol, but the development of cerebral abscesses led to this being abandoned. Cranial irradiation, together with the intrathecal methotrexate due during it, was given, but was delayed. A year after diagnosis he had a marrow relapse on treatment and subsequently died. No postmortem examination was performed.

Discussion

Fungal infection in neutropenic patients is common. In one postmortem study of young cancer patients, 23 out of 38 fatalities showed evidence of systemic fungal infection.[1]

Our patient was at particular risk of such an infection. The risk factors included prolonged neutropenia, prolonged steroid treatment, diabetes, and an indwelling Hickman catheter.[2] In addition he was on prolonged broad spectrum antibiotics, the most important factor in the aetiology of serious and fatal candidiasis. The stopping of antibiotics in those who remain febrile and neutropenic, however, carries a very high risk of serious bacterial infections.[3]

Empirical antifungal treatment is advocated for neutropenic patients with an antibiotic resistant fever.[1 4 5] Amphotericin is the only antifungal with proved efficacy in neutropenic patients and its use as a single agent in this situation is therefore recommended.[4 5] Indeed in one study nearly complete elimination of fungal infections was seen if amphotericin was started in those who remained febrile and neutropenic after a week of antibiotic treatment.[4] Starting antifungals only late in antibiotic resistant neutropenic fever is known to result in an increased mortality from fungal infection, but the optimal time to start remains uncertain.[1 5]

In our patient amphotericin was started after six days of fever resistant to antibiotics. Despite this, symptomatic presentation of mycotic cerebral abscesses occurred 12 days later and viable Candida was isolated from these three weeks after the start of amphotericin treatment. Doubt about the efficacy of amphotericin alone as empirical treatment has been expressed previously.[6]

The use of flucytosine combined with amphotericin has been suggested, not least because of its synergistic activity against Candida.[6] This combination, however, has been considered to have a number of disadvantages—namely, the need to lower the dose of amphotericin, the problems of determining flucytosine concentrations, and myelotoxicity.[5] While using this combination therapeutically in our patient none of these problems were seen. Amphotericin dosage was reasonable (1 mg/kg on alternate days), flucytosine concentrations were readily determined by our laboratories, and myelotoxicity was not an important problem. The addition of itraconazole seemed justified by the extremely high mortality previously documented for this condition.

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Hypothermia and sudden infant death syndrome

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SUMMARY We recently reported an association between recurrent episodes of severe apnoea requiring vigorous resuscitation for which no cause could be found and episodic hypothermia. Two similar cases are now reported that give further evidence of a link between hypothermia and acute life threatening episodes of apnoea.

Our first report concerned a baby boy who at the time of writing this paper was 4 years old.[1] He has had no further apnoeic attacks, but does have recurrent attacks of hypothermia (rectal temperature 32–35°C). The only new development is that he now has occasional episodes of sweating and hypoglycaemia that have been documented while he was under observation in hospital. He is being monitored at home with a skin temperature probe.

We now report two similar cases that give further evidence of an association between severe apnoea for which no cause could be found and hypothermia.

Case reports

CASE 1—A normal baby boy was born at term weighing 2270 g There was no family history of sudden infant death syndrome (SIDS) or hypothermia. He was referred from another hospital at the age of 2 months having had recurrent episodes of apparent lifelessness during sleep when he became pale, grey, cold, and limp, and had required vigorous mechanical or mouth to mouth resuscitation by his mother (a trained nurse) from the age of 4 weeks. Observations showed excessive periodic breathing when compared with age matched controls, and mild regurgitation was seen on barium swallow examination. He was treated with oral theophylline 5 mg/kg/24 hours and given a home apnoea alarm (MR-10, Graseby Dynamics Ltd). Between 1 and 12 months there was a gradual improvement both in the frequency and the severity of his attacks The apnoeic episodes stopped when he was 15 months old. From the age of 10 months he had recurrent episodes of hypothermia with a rectal temperature of less than 35°C recorded while he was under observation in hospital. These episodes were accompanied by extreme pallor and he was cold to touch (described as 'snow white' by his mother) but had no sweating. Rectal temperatures during the day were normal, and he became feverish (38°C) when he had an upper respiratory tract infection Physical examination yielded normal results, and development at the time of writing was normal.

CASE 2—A baby girl of 38 weeks' gestation was delivered by caesarian section (because of a bicornuate uterus) weighing 2892 g. She had a brief cyanotic attack at the age of 2 days, possibly associated with secretion of mucus. She was seen when she was 6 weeks old with a three week history of multiple recurrent episodes of apnoea, limpness, and cyanosis that had required vigorous resuscitation. Observations and investigations showed excessive periodic breathing, and a bradycardia of less than 90 beats/minute was recorded on cardiorespiratory tracing. She was given a home apnoea alarm but theophylline 5 mg/kg/24 hours was stopped because it made her irritable. She had recurrent apnoeic attacks requiring vigorous resuscitation every four or five weeks until she was 12 months old, and recurrent episodes of hypothermia during which she became pale and cold with a rectal temperature of less than 35°C occurred during sleep throughout the summer while she was under observation in hospital These started when she was 8 months old. Physical examination yielded normal results, and development at the time of writing was normal.

All three babies had the following measurements made, all of which yielded normal results. full blood count, erythrocyte sedimentation rate (mm in the first hour); serum urea and electrolyte concentrations; and calcium, glucose, and creatine phosphokinase concentrations. Serum glutamic oxylacetic transaminase and serum glutamic pyruvic transaminase activities, were normal as were screening tests for autoantibodies, serum concentrations of immunoglobulins, chest radiographs, cultures of cerebrospinal fluid, and Mantoux tests. Wasserman reactions were negative, as were serological tests for toxoplasma, rubella, cytomegalovirus, herpesvirus, mumps, Q fever, and psittacosis. The electrocardiograms and electroencephalograms were normal. Computed tomography of the brain yielded normal results in each case with normal copora callosa. The patient previously reported had also had magnetic resonance imaging of the brain, which was normal

Estimations of the serum concentrations of thyroxine, thyroid stimulating hormone, and prolactin (samples taken at rest) were normal. Pronounced hypoglycaemia induced by insulin produced normal serum growth hormone and cortisol concentrations. There were normal responses to thyroid releasing hormone, and the gonadotrophin responses were also normal. Cortisol concentrations showed normal diurnal variations. Early morning urine specimens concentrated normally.

Discussion

All three infants had recurrent unexplained life threatening episodes of apnoea followed later by episodes of hypothermia. This association may be more important that has previously been recognised.

We have reviewed the presentation and management of 73 cases of acute life threatening episodes of apnoea diagnosed at this hospital from 1980–84.[2] We studied all patients with episodes of lifelessness that required vigorous mechanical or mouth to mouth resuscitation to revive the infant, and in whom investigations failed to show a cause. Twelve parents (16%) stated as a presenting complaint that the child was 'cold'. This could simply be explained by the vasoconstriction that occurs in any ill child. Six children (8%), however, had recurrent severe apnoeic attacks, and three of these later developed episodic hypothermia.

Although the pathophysiology of both apnoea and hypothermia is uncertain, the most likely link between severe apnoeic attacks and temperature disturbances is a defect in hypothalamic function.[1] Episodic hypothermia is rare and usually associated with episodic hyperhidrosis and absence of the corpus callosum.[3] This link with agenesis of the corpus callosum is presumed not to be functional but developmental, perhaps occurring in the hypothalamus. One patient had gliosis and neuronal loss in the premamillary area of the hypothalamus at necropsy.[3] As the hypothalamus also controls regulation of sleep, it is interesting to note the differences in sleep patterns between normal controls and infants with severe apnoeic attacks.[4]

Neurones sensitive to local temperature extend from the hypothalamus far down into the spinal cord in an interlinked system It has been postulated that the defect causing episodic hypothermia may be below the hypothalamus. We have reported normal brain stem potentials evoked by auditory stimuli in one patient[1] This, however, does not exclude a brain stem lesion with possible effects on respiration

Altered autonomic function may affect both temperature and respiratory control, and play a part in the pathogenesis of SIDS. We have previously reported a child with poor short term variability of heart rate who died of SIDS There are, however, few data on normal controls to compare with variability in heart rate among these patients, and we could not test their autonomic function fully because they were too young.

The association between severe apnoeic attacks and SIDS has not been proved, though some of these infants have died from SIDS.[2] Abnormally high temperature has been postulated as a cause of some deaths from SIDS, despite the fact that most of the deaths occur in winter. Stress caused by cold may be a sufficient trigger for the abnormalities in fatty acid metabolism recently implicated in the pathogenesis of SIDS A defect in heat production that is metabolically mediated and accentuated by a cold environment may be a possible explanation for the increase in such deaths during the winter months. The metabolic state of these children is currently being investigated.

The presence of brown adipose tissue may also be important There is evidence that brown adipose tissue is present and functional in normal babies.[5] Aherne and Hull, quoted by Blaza, however, found that the brown adipose tissue was depleted of fat in 42 of 394 necropsies of infants who died before the age of 4 weeks. Most of the 42 deaths were due to starvation and the brown fat was only partially depleted. In six infants with injury from cold, however, they found total depletion of brown fat. A similar depletion was found in two elderly adult patients who had died of hypothermia. There were no cases of SIDS in their series.

Contrary to earlier reports, Emery and Dinsdale found less periadrenal brown fat in babies who died of SIDS compared with controls aged less than 5 months.[6] As the largest mass of brown adipose tissue in the abdomen envelops the kidneys we postulate that these infants may have been at greater risk of hypothermia.

Abnormal temperature regulation should be sought in infants with recurrent life threatening apnoeic attacks, and should be investigated closely in the search for the causes of SIDS.

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Intravenous immunoglobulin for prophylaxis of neonatal sepsis in premature infants

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SUMMARY The incidence of sepsis, mortality due to sepsis, total mortality, and minor infections was evaluated in a group of 46 premature newborn infants who were treated with intravenous immunoglobulins. They were compared with an untreated control group No significant differences were observed between the two groups.

Bacterial infections during the first few days of life remain an important cause of neonatal morbidity and mortality, especially in the premature newborn.[1] It has been reported that incidence of neonatal sepsis and its mortality rate decrease by the intravenous administration of polyvalent human gammaglobulins with an intact crystallisable fragment.[2 3] We report a randomised, controlled, blind study that was performed to determine whether intravenous immunoglobulins are able to prevent sepsis in premature newborn infants.

Patients and methods

From 1 May 1984 to 30 June 1986, 94 premature newborn infants with gestational age ≤34 weeks (mean (SD) 31 (2·5), range 26–34) or birth weight ≤1500 g (mean (SD) 1340 (235), range 870–1790) or both, were randomly assigned to a group receiving immunoglobulin treatment or to a control group (no immunoglobulin treatment). Conditions at birth that precluded enrolment of babies into the study included multiple life threatening congenital anomalies, maternal infection, and cardiopulmonary arrest. With parents' permission 46 unselected infants were given 0·5 g/kg intravenous immunoglobulin on the 1st, 2nd, 3rd, 7th, 14th, 21st, and 28th day of life. The product we used, Venogamma Polivalente (Ismunit, Pomezia, Italy), consists of human immunoglobulins obtained from the second fraction of Cohn-Oncley and treated with polyethyleneglycol (PEG 4000). It contains about 50 g/l IgG, less than 0·3% IgA, and less than 10 IU/ml IgE. The IgG subclasses are distributed as in normal serum. Besides numerous antiviral antibodies this immunoglobulin preparation contains a large range of antibacterial antibodies (for example, those to *E Coli*, Klebsiella, Pseudomonas, Streptococcus).

Serum IgG and IgM concentrations were determined before and 24 hours after every infusion of immunoglobulin by a nephelometric method. IgE was measured by radioimmunoassay. On the first day of life the following laboratory examinations were performed: culture of blood, stool, and gastric aspirate; white blood cell count (normal range $5–30\times10^9$/l), band/total neutrophils ratio (normal value <0·2); platelet count (normal value $>100\times10^9$/l); serum concentration of IgM (normal value <0·30 g/l); semiquantitative latex assay of C-reactive protein (normal value <0·008 g/l) serum fibrinogen concentration (normal range 2–2·50 g/l); haptoglobin (normal value <0·40 g/l), and serum concentration of α-1-acid glycoprotein (normal value <0·25 g/l).

These examinations were repeated when sepsis was suspected. The diagnosis of 'proven' sepsis was made when blood culture or cerebrospinal fluid culture, or both, were positive for a pathogen and were associated with clinical signs of neonatal systemic infection. The incidence of 'proven' and 'very probable' sepsis (clinical signs and changes in laboratory measurements that suggested general infection but without a positive blood culture) in the group of infants treated with immunoglobulin was compared with that of 48 newborn infants (control group) with the same gestational age, birth weight, combined antibiotic treatment (where used) and perinatal risk factors of infection.[1]

We excluded six treated infants· three underwent an exchange transfusion, two died of severe respiratory distress syndrome on the 2nd and 3rd day of life respectively after a single dose of immunoglobulin, and one had suspected prenatal infection. Eight control babies were also excluded: two had an exchange transfusion, three died of severe respiratory distress syndrome on the 3rd day of life, one died of respiratory distress syndrome and intracranial haemorrhage on the 10th day, and two had suspected prenatal infection. Sepsis was not the reason for the exchange transfusion or the cause of the death in any infant The Student's t test and χ^2 analysis were used for statistical evaluation.

Results

There were no significant differences between the

Table 1 *Clinical features of infants with 'proven' and 'very probable' sepsis*

Case No	*Sex*	*Birth weight (g)*	*Age at onset (days)*	*Clinical signs*
1	M	950	11	Convulsions, cyanosis, vomiting, apnoea
2	M	1000	4	Lethargy, cyanosis, hypotonia
3	F	970	4	Cyanosis, hypotonia,
4	M	1700	16	Apnoea, bradycardia, hypertonia
5	F	1140	5	Convulsions, lethargy, sclerema
6	F	1320	5	Lethargy, sclerema, hypotonia
7	M	440	7	Prolonged rupture of membranes hypotonia, convulsions, lethargy
8	M	1200	2	Convulsions, sclerema, hypotonia
9	F	1000	4	Cyanosis, lethargy, vomiting, apnoea
10	F	1250	16	Apnoea, lethargy, cyanosis
11	M	1100	25	Convulsions, hypotonia, cyanosis, bradycardia
12	M	1500	3	Convulsions, sclerema, hypotonia, fever
13	M	[illegible]	2	Convulsions, sclerema, hypotonia, bradycardia
14	F	[illegible]	2	Lethargy, cyanosis

mean (SD) baseline IgG concentrations in the treated (5·12 (2·31) g/l) and the untreated infants (5·99 (2·42) g/l). Although serum IgG concentrations were subject to important individual variations infusions of 0·5 g/kg intravenous immunoglobulin were sufficient to obtain serum IgG concentrations that were constantly higher than 8·00 g/l.

Table 1 summarises the main features observed in patients with sepsis. The incidence rates of proven or very probable sepsis, mortality for sepsis, and total mortality during the first 40 days of life in the infants receiving intravenous immunoglobulin were not significantly different (p>0·1) when compared with those in the control infants (table 2).

The incidence rates of minor infections (mucocutaneous candidiasis, lower urinary tract infections, subcutaneous abscess, conjunctivitis, gastroenteritis, and omphalitis) were 35% in treated and 40% in untreated newborn infants (χ^2=0·053, p>0·05) In both groups the incidences of respiratory distress syndrome (diagnosed by clinical and radiological features), hyperbilirubinaemia (plasma bilirubin concentrations >120 μmol/l), hypoglycaemia (blood glucose concentration <1·7 mmol/l), and intracranial haemorrhage (diagnosed clinically and by ultrasound) were not significantly different except for hypocalcaemia (plasma calcium concentration <2 mmol/l, 35% in treated infants *v* 7·5% in controls, p<0·001).

Table 2 *Incidence rates of sepsis and mortality in premature infants treated with intravenous immunoglobulin*

	No (%) treated infants (n=40)	*No (%) control infants (n=40)*	*p Value*
'Proven' sepsis	5 (12·5)	3 (7·5)	>0·1
'Very probable' sepsis	2 (5)	4 (10)	>0·1
Mortality for sepsis	5 (12·5)	3 (7·5)	>0·1
Total mortality	7 (17·5)	7 (17·5)	

Tolerance of the product was excellent: no newborn infant showed any local or general reaction either during or after infusions. Three infants showed a temporary increase in IgE from 10–18 to 28–38 IU/ml without concurrent side effects.

Discussion

Many premature infants have a deficiency of IgG, as the transplacental transfer of IgG from the mother increases appreciably after 32–33 weeks' gestation and the synthesis rates of immunoglobulins are very low in newborn infants. Moreover, the transplacentally acquired IgG does not protect the babies against all neonatal pathogens, and the primary

Factors indicating sepsis	*Site of positive culture*	*Causative organism*	*Outcome*
Treated			
Leukopenia, α-acid glycoprotein and IgM positive, thrombocytopenia	Blood, cerebrospinal fluid	*S epidermidis*	Died
	Blood, cerebrospinal fluid	*S aureus*	Died
C-reactive protein positive, thrombocytopenia, hyperfibrinogenaemia	Cerebrospinal fluid	*S epidermidis*	Died
C-reactive protein, haptoglobin and α-acid glycoprotein positive, thrombocytopenia	Blood	*Kl pneumonia*	Survived
Leukopenia, C-reactive protein positive, hyperfibrinogenaemia	Blood, cerebrospinal fluid	*S marcescens*	Died
C-reactive protein and α-acid glycoprotein positive, hyperfibrinogenaemia			Died
			Survived
Controls			
Leukocytosis	Blood, cerebrospinal fluid	*L monocytogenes*	Survived
Leukopenia, haptoglobin, α-acid glycoprotein and IgM positive	Blood	*P aeruginosa*	Died
Leukocytosis, C-reactive protein positive, thrombocytopenia	Blood	*S marcescens*	Survived
			Survived
Leukopenia, thrombocytopenia			Died
Leukocytosis, C-reactive protein positive			Died
Leukopenia, thrombocytopenia			Survived

antibody response to certain antigens is sluggish in neonates In addition, the transient opsonic defect is more pronounced in premature infants.[4]

For these reasons some workers have conducted controlled studies in premature infants to determine whether infections could be decreased by giving intramuscular human immune serum globulin.[5 6] These studies. however, do not provide a definite answer The availability of intravenous immunoglobulin allowed us to carry out a study giving large doses to premature infants aimed at the prevention of infections in the first month of life. The schedule we used was necessary for the achievement and maintenance of serum IgG concentrations similar to those normally observed in full term infants Nevertheless, our data show that the administration of intravenous immunoglobulin did not reduce the incidence of sepsis and mortality due to sepsis in the neonatal period. On the contrary, a recent study suggests that intravenous immunoglobulin is useful for prevention of sepsis in premature neonates, who are appreciably hypogammaglobulinaemic, in developing countries.[2] Our results are understandable in the light of the complex immunologic deficit of the newborn infant—chiefly the preterm infant—affecting all specific and non-specific defence mechanisms The immunoglobulin infusion really corrects this deficit only in part.

No adverse effects were noted after immunoglobulin transfusions in our subjects. The higher incidence of hypocalcaemia in the treated group cannot be clearly explained, but if this is confirmed it makes the routine use of intravenous immunoglobulin even more questionable.

The authors thank Miss Leonie Gane for her secretarial help

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44 *Archives of Disease in Childhood*, 1988, 63

Varicella gangrenosa

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SUMMARY A four year old girl presented with varicella gangrenosa, and haematological investigations showed a disseminated intravascular coagulation. The child subsequently developed a unilateral deep venous thrombosis. She was treated with oral steroids and intravenous heparin and made a full recovery.

Gangrene of skin and deeper tissues is an unusual complication of varicella. The term varicella gangrenosa has been applied to various conditions In 1881, Hutchinson[1] coined the term varicella gangrenosa and referred to Stokes earlier description in 1807 of gangrenous changes after chickenpox. In 1977, John described three distinct varieties: (a) moist, infective gangrene; (b) dry gangrene, secondary to arterial thrombosis; (c) purpura fulminans—that is, gangrene associated with a disseminated intravascular coagulation.[2] The child we studied presented with purpura fulminans and subsequently developed a unilateral deep venous thrombosis

Case report

A 4 year old girl developed chickenpox and initially had a relatively mild clinical progress. On the seventh day of the illness her parents noted bruising of the child's legs that was distributed over her thighs and calves. The areas affected became swollen, painful, and exquisitely tender. The child was admitted to the children's unit on the 10th day.

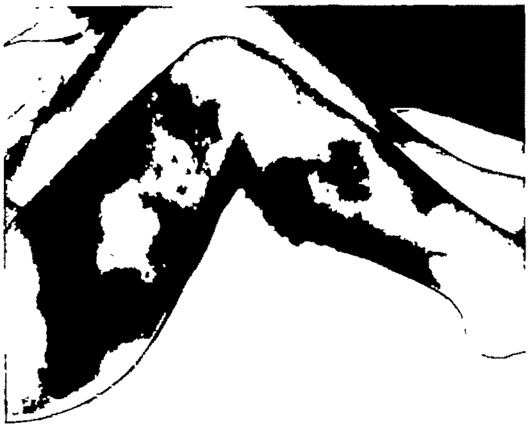

Figure *Child on the 10th day of her illness*

On admission an examination showed a child whose weight and height were both on the 55th centile for her age. The patient was in no distress and had normal vital signs. Her skin showed evidence of healing chickenpox lesions. Both limbs were swollen, with large ecchymotic areas and surrounding erythema over the anterior and lateral aspects of thighs and calves (figure). The lesions were painful and extremely tender and covered 9% of her total body surface. Lower limb pulses were normal. Examination was otherwise normal Initial haematology results showed a haemoglobin of 115 g/l, white cell count of $6\cdot6\times10^{9}$/l, platelet count of 95×10^{9}/l prothrombin ratio of 1·6 (normal 1·0) cephalin-kaolin time of 48 seconds (normal range 35–45 seconds) and fibrinogen degradation products were raised at 40 mg/l (normal range <10 mg/l). All the blood cultures during the patient's stay in hospital were negative.

Treatment was started with intravenous phenoxymethylpenicillin, as prophylaxis against infection, and oral steroids Over the next few days the ecchymotic areas became gangrenous with subsequent formation of bullae. On day 17 she complained of a painful right calf. Clinical impression of a deep venous thrombosis was confirmed on venography. Full anticoagulation treatment was started with intravenous heparin for 10 days. A further 10 weeks of anticoagulation treatment was completed with oral warfarin. Steroid doses were decreased and stopped on day 24; the phenoxymethylpenicillin was also stopped. During her subsequent hospital stay a thick eschar formed over the lesions. On separation there was evidence of re-epithelialisation at the edges with central scar tissue formation.

Discussion

Chickenpox, caused by *Herpesvirus varicella*, is in general a benign condition. Many complications, however, may occur: sepsis resulting in septicaemia; osteomyelitis; pneumonia; postinfectious encephalitis, and occasionally myelitis and polyradiculitis. Other complications are pneumonitis with nodular infiltration seen on x ray film of the chest, myocarditis and appendicitis; and haemorrhagic chickenpox where bleeding occurs into the vesicles Varicella gangrenosa is a rare complication: Barenberg and Lewis reported one case in 2000 cases of varicella seen in their hospital over 14 years. Wishik and Bullowa saw four cases in 2534 patients with varicella.

Our patient presented with the purpura fulminans variety of varicella gangrenosa. This variety consists of gangreneous skin lesions with a disseminated intravascular coagulation. Purpura fulminans was first described by Guelliot in 1884 and Henock in 1887. Hjort's criteria[3] for the diagnosis of purpura fulminans include (1) It is a disease of children (2) It is preceded by a benign disorder—usually an infection. (3) After a variable time lag bleeding into the skin occurs and spreads rapidly (4) These lesions become gangrenous with formation of bullae (5) Coagulation abnormalities compatible with disseminated intravascular coagulation may be found. (6) Thrombosis of venules and capillaries with a prevascular inflammatory infiltrate is found on investigation of the histology. This process is thought to represent a human equivalent of the generalised Shwartzman reaction of laboratory animals. There is no apparent relation between the gangrene and the severity of the varicella eruption. Indeed, as in our case, the mildness of the eruption has been noted [4] In Spicer's literature review of 100 cases, varicella was the third most common preceeding illness, 19% had an entire extremity amputated, and the overall mortality was 35% [5] Our patient, who was affected extensively in both lower limbs, made a full recovery with minimal scar tissue formation

Because of the rarity of this condition no definitive treatment can be recommended. Treatment in the acute phase is largely supportive. Heparin treatment has been used with some good results The dose and duration of treatment vary widely, but most reports suggest a high dose over at least three weeks. Controlling the coagulopathy does not affect the ecchymosis or the incidence of gangrene and there are many reports of unfavourable experiences.[6] Steroids have been used in many cases with varied results Our patient responded well to steroids and heparin without resort to skin grafting or amputation

We thank Dr D Buckley, consultant dermatologist, and Mr J McCann, plastic surgeon, for their advice during this case and Miss Ann-Marie O'Connor for secretarial help

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Controversy follow up

Sexual abuse—the final word?

When differing views are strongly held there is inevitably a tendency to confuse the facts underlying an opinion with the emotional issues that surround the controversy. While tabloid and television journalism thrives on exploiting this confusion it is the responsibility of a scientific journal to portray the underlying facts of an argument as far as possible and to let readers judge for themselves the merits of each of the opinions expressed. Highlighting controversial issues in the journal and allowing experts with differing opinions to explain their views is one way of strengthening the scientific basis of paediatrics.

Contributions to the Controversy section are normally accepted on the basis that a commentary will be commissioned and seen by the original author who will be invited to provide a 'summing up' argument. However, in the circumstances surrounding this particular controversy Dr Roberts provided her commentary on the basis that it would not be followed by a further contribution by Drs Hobbs and Wynne, who would nonetheless have the correspondence column available to them if they wished to reply. We showed Drs Hobbs and Wynne the commentary to allow them priority through the correspondence column of a forthcoming issue. In the event their response came so quickly it was inadvertently included immediately after Dr Roberts commentary.

Published articles, like intravenous injections, cannot be withdrawn. We have therefore invited Dr Roberts to provide a further comment which is published below

EDITORS

Dr Roberts writes—

I believe that buggery is *not* a 'common, underdiagnosed form of child abuse.' Dr Arnon Bentovim, in his evidence to the Cleveland Child Abuse Inquiry, gave a figure of 1–2% anal dilatation in his cases. Patients with psychosexual problems related to child sexual abuse do not describe anal abuse in most cases (Dr May Duddle, personal communication). There is an astonishing difference between the figures of the Manchester women police surgeons and those of Wynne and Hobbs which requires explanation. The character of the two large northern cities is similar but the Manchester figures are of children seen mainly at the request of the police and where there is usually a complaint from the child. Though in 60% to 70% of them no medical evidence can be found, they are probably mostly genuine cases of sexual abuse We have found anal signs of buggery in only 3·3% of 879 children seen in the past two years, 37% of whom were under the age of 5 and all of whom were carefully examined from top to toe. In these cases there is a very much smaller proportion of children suffering physical abuse and neglect, though many of them are rather poorly parented. In contrast, the Leeds figures include many more children where physical abuse and neglect are present and I believe that in many of these cases spurious and false signs, which have been wrongly held to indicate sexual abuse, particularly anal abuse, have been found.

Perhaps it has been thought that it does not matter too much if another problem is added to the list in these poor and deprived children, though for the individual families suspected of sexual abuse as well as physical abuse, it does But when these erroneous thoughts are then extrapolated to the general population and used to make a diagnosis of sexual abuse in children referred to outpatients for instance, it becomes a matter for concern. It does not aid the cause of the many sexually abused children in our society who desperately need our help for doctors to make the diagnosis on emotional and unscientific grounds.

Anal dilatation is an odd and intriguing phenomenon for which there is no satisfactory explanation. It has many similarities to yawning, which occurs for a number of reasons that are ill understood, at the opposite end of the alimentary tract. If it is a learned response to pain or discomfort, one must question why people with anal fissure do not learn it and why it is so variable and is extinguished so quickly. It may well occur more readily in the anus of the child than the adult and a number of factors which cause irritation of the anal area may perhaps cause the anus to become hypersensitive and to react in this way. It has been described in many forensic texts, and usually occurs in adult sodomites, and paediatricians quite rightly advise caution in the extrapolation of adult findings to children. An interesting point, however, is that though many adult women who have been subjected to buggery as part of a rape or repeated buggery in a previous relationship are examined by the Manchester women police surgeons, anal dilatation has not been observed in such cases, though it has been seen rarely a few days after buggery has occurred in boys and girls.

Very much more work must be done to understand the normal and abnormal anus of the child, and in the meantime the greatest caution must be observed in making a diagnosis of anal abuse without a clear and unprompted history from the child.

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Current topic

Copper deficiency and non-accidental injury

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When parents are brought before the courts accused of causing their children serious injury it is imperative that a strictly medical cause for the injuries should not be overlooked. Unfortunately the adversarial nature of court proceedings often leads those involved, quite understandably, to give a higher priority to winning the case than to discovering the truth. However in child care proceedings finding the truth is often more important than winning the case as it is as much a disaster for a child to be wrongly removed from the care of loving parents as it is to return a child to guilty parents who might further injure or kill him.

In recent years it has been increasingly common to hear the defence that the child's injuries were the result of copper deficiency. As copper deficiency does cause bone disease and may present in the first two years with fractures it is essential that the diagnosis is considered and the appropriate tests are performed at the time that the child first presents with his or her injuries. If this is done, then a case of copper deficiency is not likely to be missed, and a defence of copper deficiency will not prevail merely for lack of evidence to the contrary. The purpose of this paper is to draw attention to the existence of copper deficiency in infants and to review what is known about it, so that the diagnosis will not be overlooked.

Biochemical background[1]

In 1928 Hart *et al*[2] in an elegant series of experiments[3] demonstrated that copper was essential for erythropoiesis in the rat. It is now known that copper is a component of several enzymes, including cytochrome C oxidase, superoxide dismutase, caeruloplasmin, tyrosinase, lysyl oxidase, and dopamine β hydroxylase. These enzymes generally bind between 1 and 3 g atoms of copper per mole and the presence of copper is essential for their activity. Many of them engage in oxidation reduction reactions.

UNITS OF MEASUREMENT

Because most of the papers quoted in this review did not use SI units, it has been decided to give the values as reported in the original papers. The atomic weight of copper is 63·5, so 1·0 μg copper/dl=0·157 mmol/l. Because the molecular weight of caeruloplasmin is not known precisely the best SI unit of concentration is g/l

Copper deficiency

The features of copper deficiency given below are based on 52 cases reported in the paediatric literature since 1956.[5–27] The reports vary considerably in the amount of detail given, depending on the extent of knowledge at the time they were written, the diagnostic facilities available, the analytical methods used, and the purpose of the report (that is, mainly radiological, mainly biochemical, or mainly clinical). Nevertheless though the amount of data given are variable, and in some cases are possibly open to other interpretations, there is no conflict between any of the reports, which makes it probable that they are all describing, in different ways, the same condition. For this reason I have included all cases where there are sufficient data to analyse.

The characteristics of copper deficiency in infants are summarised below.

SYNDROME OF COPPER DEFICIENCY IN INFANTS

- Psychomotor retardation.
- Hypotonia.
- Hypopigmentation.
- Prominent scalp veins in palpable periosteal depressions.
- Radiological changes of osteoporosis, blurring and cupping of the metaphyses, sickle shaped metaphyseal spur formation, subperiosteal new bone formation, and fractures.
- Pallor.
- Sideroblastic anaemia, resistant to iron

treatment. Bone marrow shows vacuolated erythroid and myeloid cells with iron deposition in the vacuoles.

- Hepatosplenomegaly (a feature of sideroblastic anaemia).
- Neutropenia, usually <1·0×10^9/l.
- Plasma copper concentration usually <40 µg/dl, and caeruloplasmin <13 mg/dl.

Many of the features can be explained on the basis of deficiency of particular copper enzymes. The prominent scalp veins and bone changes are thought to result from impaired collagen and elastin cross linking due to depressed lysyl oxidase activity. The consequent reduction in strength of the bone collagen causes fragile bones that fracture easily. The hypopigmentation is probably due to depressed tyrosinase activity and impaired melanin synthesis. The sideroblastic anaemia is less well understood, but there seems to be depression of iron transport into the mitochondria, and impaired incorporation of iron into protoporphyrin IX within the mitochondria.[3] The cause of the neutropenia is not understood.

Diagnosis of copper deficiency

If it is thought that fractures and changes in the growing ends of long bones may be due to copper deficiency, the diagnosis cannot be established for certain without quite detailed investigations, and these are often lacking in cases where non-accidental injury is suspected. However consideration of what is known about copper deficiency will certainly indicate if the diagnosis is at all probable. Of the 52 cases reported below, 51 were under 5 years of age,[5,6,8–27] and 49 were 18 months or less at the time of diagnosis.[5,6,8–10,12–27] Those classed as full term include seven infants who are presumed to be full term but whose birth weight or gestation are not given. The low birthweight infants are infants whose birth weight is given or who are stated to be of low birth weight (<2500 g). Their median birth weight was 1040 g (range 680–2300 g).

Predisposing factors

In the published reports one or more of a number of predisposing factors have been present in every case. These are listed below.

(1) LOW BIRTH WEIGHT

Forty per cent of reported cases were less than 2500 g at birth.[5,6,9,10,13,21,22,24,25,27] Low birthweight infants have lower body stores of copper at birth than full term infants (3·5 mg/kg fat free body weight at 20 weeks' gestation rising to 4·8 mg/kg fat free body weight at term).[28] During the last three months of gestation they accumulate copper at a rate of about 51 µg/kg/day.[29] If, however, they are born prematurely they will be in negative copper balance for up to six weeks after birth.[30] Full term infants also have a period of negative balance after birth.[31] Though this will cause a transient decline in the total body copper it is not thought to cause copper deficiency if the subsequent dietary copper intake is sufficient. The full term infant at least has a high concentration of copper in the liver[32,33] and the current evidence suggests that full term infants have stores sufficient for at least five months and low birthweight infants for at least two months.

Causes of bone mineral deficiency in low birthweight infants

The smaller low birthweight infants invariably experience a decline in the concentration of bone mineral after birth when compared with a fetus of equivalent gestation *in utero*. This occurs because they cannot absorb and retain the amount of calcium and phosphorus that would be laid down had they remained *in utero*.[34] If they are fed breast milk there is an absolute dietary deficiency of calcium as on maximum intake they would receive only about half the intrauterine accumulation rate. Because there is insufficient phosphorus in breast milk low birthweight infants fed breast milk tend also to develop phosphate deficiency rickets,[35] unless they are given phosphate supplements. They therefore develop weak bones and are prone to fractures of ribs and long bones even if they do not have copper deficiency. They do not, however, develop skull fractures.

(2) DIETARY DEFICIENCY OF COPPER

Total parenteral nutrition

Twenty three per cent of the infants received total parenteral nutrition.[6,8,15,16,17,19,24,26] In eight of the cases the solutions were deficient in copper. In the three other cases copper had been added to the solution,[24] but other predisposing causes—namely, prematurity and copper deficient milk—were present.

Copper deficient milk

Fifty four per cent of infants were fed exclusively cows' milk or predominantly cows' milk with very short periods of breast feeding.[6,10,11,14,18,21,23] A further 12% were fed formula milks[5,9,12,13,27] of which at least one was copper deficient.[5] The changes in the concentration of copper in breast milk are given in tables 1 and 2. Cows' milk has a much lower concentration of copper in it than breast

Table 1 *Changes in concentration of copper in human milk during lactation*[36 37]

Time postpartum	*Copper concentration*	
	µg/dl	*(SD)*
2–5 days	45	(13)
6–13 days	67	(19)
15–28 days	58	(8)
2 Months	61	(15)
3 Months	42	(22)
4–7 Months	29	(23)

Table 2 *Comparison of changes in copper concentration in milk from mothers of full term and preterm infants*[38]

Time postpartum	*Copper concentration µg/d (SD)*	
	Full term infants	*Low birthweight infants*
3–5 Days	72 (13)	83 (21)
8–10 Days	73 (21)	78 (18)
12–17 Days	57 (8)	75 (24)
28–30 Days	58 (9)	63 (14)

milk. The copper content of cows' milk is stated to be 20 µg/dl range 10–30 µg/dl.[39] and in one report values as low as 5·7 µg/dl were found.[21] Copper deficiency has never been described in an infant fed exclusively on breast milk, or a full term infant fed a formula known to contain adequate amounts of copper that is, >40 µg/dl.

(3) ANTECEDENT MALNUTRITION
Twenty five per cent of the cases suffered from severe antecedent malnutrition. This was due to a starvation diet[10] or malabsorption and diarrhoea,[8 25] giardiasis,[10] a probable disaccharidase deficiency,[11] short bowel[16 19 26] or coeliac disease.[12] Vomiting was reported in 13% of cases and probably contributed to the aetiology of the malnutrition [6 10 11 18 23]

(4) PERITONEAL DIALYSIS
There is one report of a 16 year old with cystinosis who developed copper deficiency after several years of ambulatory peritoneal dialysis.[7]

Clinical features

(1) AGE AT PRESENTATION (Infants <18 months at diagnosis)
The median age at presentation for full term infants[7 8 10–12 14–21 23 26] was 8·3 (range 5–18) months and for the low birthweight infants was 3·0 (range 2·2–15) months.[3 5 9 10 13 21–25 27] This difference presumably reflects the difference in the body stores of copper present at birth.

(2) HISTORY AND PHYSICAL EXAMINATION
Details of physical examination were reported in only 14 of the 52 cases.[5 6 10 12 14 18 20 24 25] In these 14 infants hypotonia was reported in 43% (lax joints in one case), hypopigmentation in 29%, psychomotor retardation in 21%, skin rash in 21%, dilated veins in 15%, and hepatosplenomegaly in 15%. There was no mention of bruising or of blue sclerae in any of the 52 cases, and no case had cerebral haemorrhage. In no case was there any evidence of copper deficiency in the mother during pregnancy, and there was no case where there was any family history of copper deficiency.

(3) INFECTION
Specific infections are mentioned in six cases. They include two cases of congenital syphilis and tuberculosis,[10] one case of bronchopneumonia,[27] one case of infected central venous catheter used for total parenteral nutrition,[16] one of otitis media,[18] and the case of giardiasis mentioned above.[10] Others are described as 'mild and non specific'.[21] These cannot easily be construed as being a consequence of copper deficiency and the giardiasis probably contributed to it.

Plasma copper and caeruloplasmin

In the full term infants the median plasma copper was 37 µg/dl (range 7–89), and the median caeruloplasmin was 3·0 mg/dl (range 0·4–13·0) In the low birthweight infants the median plasma copper was 28 µg/dl and the median caeruloplasmin was 3·0 mg/dl (range 0·0–4·0). During the last 30 years the analytical methods have improved, and most of the higher values in the literature date from the earlier period 1956–70. In the more recent reports where modern methods (that is, atomic absorption spectrophotometry) were used no case of copper deficiency has been reported in a full term infant with a plasma copper of more than 43 µg/dl and in a low birthweight infant with a plasma copper of more than 33 µg/dl.

PLASMA COPPER AND FRACTURES
The median plasma copper concentration in those infants who had fractures (see below) was 14·5 µg/dl (range 4·5–68). Only one value was over 33 µg/dl and this dated from 1964 when analytical methods were not so reliable.

NORMAL PLASMA COPPER
The plasma copper concentration in pregnant and

non-pregnant women and changes in plasma copper in full term infants and preterm infants are given in tables 3, 4, and 5. In evaluating the plasma copper it is important to take into account the birth weight and the age of the baby as the plasma copper and caeruloplasmin both vary with postnatal age and gestation. In the newborn about 85% of the plasma copper is bound to caeruloplasmin and the remainder is probably bound to the serum albumin and complexed with aminoacids. The plasma copper and caeruloplasmin are both low at birth and rise to adult values at about 6 months of age (table 3). The plasma concentrations in low birthweight infants are about the same as full term infants at birth but rise more slowly (table 4). The values shown in table 4 were the same whether the infants were fed a formula containing 40 μg/dl of copper or one containing 167 μg/dl of copper.[46] It therefore seems likely that these values are representative of plasma copper concentrations to be found in low birthweight infants who are not copper deficient. The normal range would therefore be the mean (2 SD). From these data it can be seen that a small preterm infant of 2–3 months may have a very much lower plasma copper concentration than a full term infant of same postnatal age and yet not have copper deficiency.

Table 3 *Changes in serum copper with age in full term infants*[40 41 42]

Postnatal age	*Plasma copper concentration*	
	μg/dl	*(SD)*
Cord blood	29	(11)
5 Days	47	(9)
1 Month	63	(17)
3 Months	81	(17)
5 Months	104	(25)
6–12 Months	111	(19)
6–12 Years	109	(17)

Table 4 *Changes in plasma copper in preterm infants*[43]

Postconceptional age (weeks)	*Plasma copper concentration*	
	μg/dl	*(SD)*
25–28	29	(17)
29–30	27	(15)
31–32	32	(18)
33–34	36	(15)
35–36	39	(14)
37–38	47	(24)
39–40	53	(12)
41–42	60	(12)
43–44	70	(28)
45–46	65	(16)
47–48	82	(18)

Table 5 *Copper and caeruloplasmin concentrations in maternal and fetal blood*[40 44 45]

	Copper concentration	*Caeruloplasmin concentration*
	μg/dl (SD)	*mg/dl (SD)*
Male plasma	92 (12)	31 (4)
Female plasma (non-pregnant)	107 (23)	31 (5)
Female plasma (on oral contraceptives)	221 (62)	57 (21)
Pregnant plasma taken at 16 weeks	162 (27)	71 (24)
Pregnant plasma taken at 36 weeks	192 (24)	
Pregnant serum taken at term	221 (54)	91 (13)
Cord blood serum taken at term	29 (11)	10 (6)

Haematological changes

ANAEMIA

Ninety two per cent of the full term infants and 85% of the low birthweight infants had a haemoglobin concentration of less than 100 g/l. The median haemoglobin of the full term infants was 49 g/l (range 26–136) and of the low birthweight infants was 70 g/l (range 27–119). Examination of the bone marrow showed typically maturation arrest with marked vacuolisation in the erythroid and myeloid cells with numerous ringed sideroblasts.[5] The picture is not therefore one of iron deficiency though in some cases, notably those fed cows' milk, the

Table 6 *Bone changes reported in copper deficiency**

	No (%) Full term infants	*No (%) Low birth weight infants*
Fractures	*(n=31)*	*(n=20)*
Fracture of long bone(s)	3 (10)	5 (25)
Fracture of epiphyseal plate(s)	2 (6)	2 (10)
Fracture of ribs	—	3 (15)
Metaphysial chip fracture	1 (3)	—
Fracture of the skull	—	—
Other changes	*(n=14)*	*(n=13)*
Osteoporosis	8 (57)	11 (85)
Fraying and cupping of the metaphyses	9 (64)	11 (85)
Spurs	8 (57)	—
Subperiosteal new bone formation	6 (43)	7 (54)

*The incidence of fractures is for the whole group, and the incidence of other changes is for the group in whom the results of *x* rays were reported Note that some infants had more than one fracture reticulocyte response to iron treatment showed that iron deficiency did coexist with the copper deficiency. The median plasma iron concentration in the full term infants was 20 µg/dl (range 4–116) and in the low birthweight infants was 16 µg/dl (range 10–78). The higher median haemoglobin concentration in the low birthweight infants was probably attributable to the fact that they were transfused.

NEUTROPENIA

A neutropenia of less than $1{\cdot}0\times10^9$/l was found in 34% of the infants in whom the results of a white blood cell count were reported (n=25)[5–7 9 10–16 18 20 24–27] and all these infants had a neutrophil count less than $2{\cdot}0\times10^9$/l. There were no differences between the low birthweight infants and the full term infants. The median neutrophil count was $0{\cdot}376\times10^9$/l (range 0·049–1·9). As in infants with fractures the median neutrophil count (n=9) was $0{\cdot}393\times10^9$/l (range 0·08–1·2) it is doubtful if the diagnosis of copper deficiency of sufficient severity to cause fractures should be considered in the absence of neutropenia.

Bone disease

The results of *x* ray examination of the bones of infants with copper deficiency are summarised in table 6. Fractures were found in 11 cases.[5 9 10 11 13 14 17 19 25 27] The percentage incidence of fractures is based on the whole group of infants (n=51) on the supposition that a fracture is unlikely to be missed clinically. The percentage incidence of the other changes are based only on the cases where bone changes on *x* ray are reported (n=27)[5 6 8–11 13–20 24–27] because many of the findings are not evident clinically and might not be detected if an *x* ray film was not taken. The subperiosteal new bone formation can be very extensive and reflect organising subperiosteal haemorrhage,[17 19 25] in other cases it can be quite inconspicuous, and may simply reflect normal bone growth, particularly in premature infants.

DISTINGUISHING BONE CHANGES IN COPPER DEFICIENCY FROM THOSE IN NON-ACCIDENTAL INJURY

The most important thing to keep in mind is that both a fracture and a subperiosteal haemorrhage are evidence that a force has been applied to a bone, but unless the magnitude of the force is known (and this is sometimes in dispute), their presence gives no information as to the strength of the bone, so they cannot be used as evidence for the presence or absence of copper deficiency. They are neutral in that respect. Evidence for the presence of bone disease must be sought elsewhere.

Low birthweight infants, because they have small slender bones and experience difficulty in absorbing and retaining bone mineral at a rate that is comparable with the *in utero* accumulation rate, have a higher incidence of osteoporosis and fractures than full term infants even in the absence of copper deficiency.

The features that should alert one to the diagnosis of copper deficiency are the cupping and fraying of the metaphysis of the long bones, and the sickle shaped metaphyseal spurs, which sometimes fracture, and seem to be very characteristic of copper deficiency. The best photographs of these appearances are to be found in the paper by Grünebaum *et al.*[14] As copper deficiency is a metabolic bone disease it will affect the entire skeleton in a symmetrical manner, being particularly evident in the most rapidly growing bone ends, namely the wrists and the knees. The proximal ends of the femora and humeri are also affected as are the costochondral junctions, which may enlarge. The bone age seems frequently to be retarded.[14] The findings on *x* ray examination may be confused with those of scurvy or rickets but the help of an experienced radiologist and the characteristic biochemistry and haematology should make the diagnosis fairly straight forward. The age at diagnosis in full term infants with fractures ranged from 6·5 to 60 months (median 9 months) whereas the age at diagnosis in the low birthweight infants with fractures ranged from 2·2 to 7·0 months (median 2·8 months). Therefore when a full term infant of less than 6·5 months or a preterm infant of less than 2·2 months presents with fractures copper deficiency is not a likely diagnosis. It is noteworthy that skull fractures have never been reported in copper deficiency and neither have rib fractures in full term infants with copper deficiency. Fractures have never been reported as a late sequel to copper deficiency.

In contrast the bone changes in non-accidental injury are usually unsymmetrical and where they are numerous they are often of different stages of healing indicating that they are injuries that have taken place over a period of time. Though individually a metaphyseal chip fracture or subperiosteal haemorrhage may resemble those seen in copper deficiency, they occur against a background of an otherwise radiologically normal skeleton, without any retardation of the bone age.

Response to treatment

In the reported cases the median copper intake used in treatment was 290 µg copper/kg/day (range 63–800) and in one case on total parenteral nutrition, intravenous treatment was given in a dose of 50 µg/kg/day. Treatment resulted in a reticulocyte response within 1–2 weeks, median 4·6% (range 2–14%), and the neutrophils rose above $1{\cdot}0\times10^9$/l within about five days. Healing of the fractures and resolution of the other bone changes were well advanced after 30 days As some of the infants recovered without any special treatment other than introducing a more varied diet with a higher copper content, it is possible that the occasional infant may pass through a period of transient deficiency and recover spontaneously as his repertoire of food increases, without ever being diagnosed.

Genetic diseases of copper metabolism

Though there are a number of diseases of copper metabolism described in experimental animals there are only two that have been established with certainty in man, Menkes' disease, and Wilson's disease. The only one to be confused with copper deficiency is Menkes' disease.[47] This is an X linked recessive condition that only occurs in boys Though it has many of the features of dietary copper deficiency including the low plasma copper and caeruloplasmin, and the bone changes, anaemia and neutropenia do not occur. Intracranial haemorrhages do occur in patients with Menkes' disease but have never been reported in dietary copper deficiency in infants. The presence of convulsions and hypothermia and the relentless downhill course with death usually within two years makes confusion unlikely. A syndrome of benign familial copper deficiency has been described in a single family.[48] The propositus at 21 months of age had fair hair, a seborrhoeic rash on his face, convulsions, and bone changes resembling those of copper deficiency. There were no fractures and no features suggestive of non-accidental injury. The plasma copper was low but the caeruloplasmin concentration was normal.[49] The fits and the rash responded to treatment with copper.

Adult copper deficiency

This has not to my knowledge been described in a pregnant woman and the cases in the literature have been found in patients on total parenteral nutrition with inadequate concentrations of copper in the solutions, and in patients with bowel resections.[50 51]

Copper content of milks

There is some uncertainty about the copper content of formulas sold for infant feeding in the United Kingdom and Europe. Table 7 gives the mean values and range of copper found in formulas in different countries The data are mainly from Lonnerdal *et al*[52] but the data on English milks are my own unpublished data from 1982. It can be seen that some formulas have a very low copper content and at 150 ml/kg/day would supply much less than the amount supplied by breast milk (table 1 and 2) or the recommended requirements for full term infants (see summary below). If copper is to be added to infant formulas in manufacture then the milk powder must be packed under nitrogen to prevent oxidation of the fatty acids, which turns the milk rancid. Today most milks are packed in this way.

Table 7 *Copper concentration of different infant formulas*

Country of origin	*No of samples*	*Copper concentration µg/dl*	
		Mean	*Range*
United States of America*	14	48	31–65
Sweden*	12	18	3–70
West Germany*	12	20	1–135
Japan*	8	6	2–15
The Netherlands*	2	28	14–43
United Kingdom*	2	14	5–23
Fullterm formula†	9	18	1–47
Preterm†	3	68	62–73
Soy formula†	1	51	
France*	2	12	5–20
Norway*	1	25	

*Reference 52, †JCL Shaw, unpublished data analyses performed in 1982

Recommendations of various bodies

(1) EUROPEAN SOCIETY FOR PAEDIATRIC GASTROENTEROLOGY AND NUTRITION (ESPGAN) COMMITTEE ON NUTRITION (1977)[53] (Full term infants)

Minimum value 30 µg/100 kcal (20 µg/100 ml).

(2) DEPARTMENT OF HEALTH AND SOCIAL SECURITY (DHSS) (1980)[54] (Full term infants)

'It seems likely that the amount of copper in infant feeds should be not more and not less than the amounts present on average in mature human and cows' milk, that is to say not less than 10 µg and not more than 60 µg/100 ml, but at present sufficient information is not available for a recommendation to be made'.

(3) AMERICAN ACADEMY OF PEDIATRICS (1976)[55] (Full term infants)

Minimum intake 90 µg/100 kcal.

(4) AMERICAN ACADEMY OF PEDIATRICS (1977)[56] (Low birth weight infants)

'Recent data suggests that an intake of 90 µg/100 kcal is desirable'.

(5) CANADIAN PAEDIATRIC SOCIETY: (1981)[57]

'It has been suggested that low birthweight infants require 90 µg/100 kcal to avoid copper depletion'.

(6) AMERICAN ACADEMY OF PEDIATRICS (1985)[58] (Low birth weight infants)

'90 µg/100 kcal continues to be appropriate'.

Unfortunately the recommendations of the DHSS (see above) were framed in such a way that the manufacturers felt that they did not necessarily have to fortify formulas with copper. As a result the copper content of some infant formulas sold in the United Kingdom in the past was less than 10 µg/dl,[59] and in some samples of milk copper was almost undetectable (JCL Shaw, unpublished data). However at the present time SMA, Cow and Gate Premium, and Farley Health Product Milks (Osterfeed, Ostermilk Complete, and Ostermilk II) all contain enough copper (roughly 40 µg/dl), and have done since at least 1983. The Milupa products on the other hand contain more variable amounts of copper. The manufacturers claim that Aptamil contains 45 µg/dl, Milumil 26·2 µg/dl, and Preaptamil, the formula designed for preterm infants, only 10 µg/dl.

It is therefore evident that while most milks used for infant feeding in the United Kingdom contain what is believed to be sufficient copper some do not. The most striking example is Preaptamil and this milk is soon to be replaced by a milk with a higher copper content. Unless circumstances have changed since the report of Lönnerdal *et al*[52] there may also still be milks marketed on the continent of Europe that contain insufficient copper.

Copper deficiency and non-accidental injury

Copper deficiency should be considered in the differential diagnosis of bone fractures in young infants. Once copper deficiency has been proposed it cannot be refuted as a cause with complete certainty unless there are detailed radiographs of the whole skeleton, measurements of plasma copper, caeruloplasmin, haemoglobin and differential white cell count, and possibly bone marrow. The presence of a predisposing cause, the characteristic age at onset, and a response to treatment add to the security of the diagnosis. However it is possible, in the absence of specific diagnostic tests, to determine the probability that a correct diagnosis has been made.

If the patient is a full term infant, under 5 months of age, who has been breast fed, or has received a milk with a copper concentration of 40 µg/dl or more then the diagnosis is unlikely. Such a case has never been described. The absence of the predisposing conditions mentioned above (prematurity, preceding malnutrition, a deficient copper intake, malabsorption) make the diagnosis even more unlikely. If the copper deficiency is sufficiently severe to cause fractures then some of the other clinical features (for example, skin rash, hypotonia, psychomotor retardation, or hypopigmentation) are likely to be present, together with anaemia, neutropenia, and a low plasma copper concentration.

Neither skull fractures nor cerebral haemorrhage have ever been described in infants with copper deficiency, and rib fractures have never been described in full term infants with copper deficiency. The presence of any of these points to another diagnosis. The demonstration of normal bones, and in particular wrists and knees, makes the diagnosis very unlikely. Obviously if the other features of copper deficiency (hypocupraemia, low caeruloplasmin neutropenia, and sideroblastic anaemia) are absent then the diagnosis can be confidently ruled out.

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Archives of Disease in Childhood, 1988, **63,** 456–458

Special report

Facts for teachers of children with cancer

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SUMMARY As the prospects of cure for children with cancer increase, the long term consequences of treatment and the quality of life experienced by survivors assume greater importance. Strategies to encourage early return to school after diagnosis are of considerable importance both educationally and socially, but teachers require information to help them facilitate the child's return. The extent to which professional contact is fostered between children's cancer centres and the education service is the subject of this short survey.

The prospects of cure for children with cancer are steadily improving. Approximately 1200–1400 children are diagnosed with cancer each year in the United Kingdom[1] yet almost 60% of children treated at institutions affiliated to the United Kingdom Children's Cancer Study Group (UKCCSG) are alive five years from diagnosis[2] and most of these will be long term survivors. Median survival, even among children who ultimately die of their disease, has been prolonged by modern multimodal treatment.[3] These improving results bring with them concerns about the quality of life achieved by children with cancer, both during and after treatment, and physical, psychological, and social consequences are now being described in long term survivors.[4] The consequences vary, depending on the type of malignancy, the treatment used, and the age of the child at diagnosis.

Whether a child's cancer is diagnosed before or during school life, attending school provides a common experience. School provides organisation in children's lives. It develops the child intellectually, physically and, through social contact, it encourages emotional maturity. Early return to school provides a return towards normality for the child with cancer and the effects of school absenteeism are reported by long term survivors to be among the most important consequences of having had cancer.[5] High rates of absenteeism found among children with cancer are only partly explained by clinic visits, hospitalisation, or acute illness and previous studies have shown that the child encounters many difficulties in returning to school after diagnosis[6 7] Anxieties and embarrassment arising from their illness, together with the frequent development of a dependent, protective relationship between parent and child,[8] may reinforce absence from school.

Attempts to modify school attendance patterns have focused on school staff and surveys have shown that teachers need more information about childhood cancer and its specific implications for schooling.[9] In our own unit, which serves as the paediatric oncology centre for the West Midlands health region, a leaflet written specifically for teachers (and parents), addressing some of the issues involved in returning the child to school, is used as the principle way of providing appropriate information for schools. This is sent, with parental consent, to the schools of all newly diagnosed children, by the hospital school, which provides a point of professional contact to which a child's teacher can refer, in addition to contact with the medical staff. The information contained provides an overview of cancer in children, a perspective on prognosis with modern treatment, and a discussion of the potential hazards of contact with infectious disease. It addresses the anxieties experienced by children on their return to school, with suggestions for helping reintegration and discusses the appropriate use of the home teaching service. The leaflet appears to be well received. We recently wrote to all paediatric oncology centres in the United Kingdom requesting information about their contact with schools in order to assess the pattern of school liaison available for children with cancer in this country.

Methods

In order to assess current strategies for liaising with the schools of children with cancer, we wrote to the other 18 regional paediatric oncology centres in the United Kingdom asking them what contact they had with teachers and for copies of any written information they provided for schools. We analysed the contents of the documents and other services provided by centres for teachers and schools.

Results

Replies were received from 13 (72%) of the 18 centres contacted. Analysis indicated that the information provided fell into three main categories and the data included information from all the centres which responded, including our own.

GENERAL INFORMATION LEAFLETS

Six (43%) centres sent schools copies of information pamphlets written for families— such as those issued by the Leukaemia Research Fund—but did not have any specific information for distribution to teachers. One centre sent copies of booklets written for children themselves, which explained the disease, its treatment, and common emotional problems in general terms suitable for younger children. All centres emphasised the need for personal contact with teachers.

MEETINGS WITH TEACHERS

One centre held meetings with teachers of newly diagnosed children on a regular basis

SPECIFIC INFORMATION FOR SCHOOLS

Five (36%) centres, including our own, used leaflets, written locally but specifically designed for teachers. The information they contained included the following points (number in square brackets refers to the number of booklets referring to each point):

(1) *Overview of childhood cancer*: it was noted that (a) cancer in children is relatively uncommon but chances of survival are improving with modern treatment [4]; and (b) cancer is not infectious and affected children pose no health risk to their classmates [5]; (c) the types of treatment used (for example, chemotherapy, radiotherapy) and the more obvious possible side effects (for example, hair loss, change in weight) were explained [5].

(2) *Infection risks and medical problems at school*: there was (a) emphasis on the importance of measles and chicken pox contacts [5]; (b) emphasis on the small risk of medical problems arising at school [1]; and (c) advice on the management of fever and bruising [1].

(3) *Children's knowledge of their disease*: it was explained that children know the nature of their disease and that their questions should be answered honestly in an age appropriate way [2].

(4) *School attendance*: (a) it was explained that absence for medical reasons may be unavoidable at times but that the child's or parent's anxieties may reinforce absenteeism at other times [5]; and (b) that an early return to school is important to the psychological well being of the child [5].

(5) *Academic performance*: (a) it was emphasised that it was important to maximise the child's potential and that inappropriately reduced expectation is a common finding among both parents and teachers [5]; (b) the provisions for schooling in hospital and at home were explained [3], and (c) an invitation for teachers to contact the oncology department to discuss details of the child's school performance was made [3].

(6) *Other points made were*: (a) advice to teachers in explaining the illness to the child's peers at school [3]; (b) an explanation that the patient's siblings may also experience emotional difficulties and that their teachers should also be informed [2]; and (c) a discussion of death and dying [1].

Discussion

Teachers faced with the diagnosis of cancer in one of their pupils have to confront several problems First, on an emotional level, they may greet the news with the same mixture of emotions as do the family or the child's close friends. Second, they encounter rational anxieties which relate to their lack of knowledge about the situation. The child or his classmates may ask questions for which they are unprepared or they are unwilling to answer, raising concerns about how much the child has been told of his disease and prognosis They may be concerned that the child could become seriously ill while in their care, or acquire infection from contacts with classmates, for which they would feel responsible. Finally, the teacher faces a conflict between the care of the individual—the child with cancer—and the needs of the rest of the class.

Many of these concerns can be addressed by 'educating the educators' and most children's cancer centres recognise the need to liaise with schools and to provide information for teachers as a means of facilitating their patients' return to the classroom The results of our brief survey show that efforts to achieve this in the United Kingdom are variable. Although all centres acknowledged the importance of information for schools, and many make considerable efforts to contact teachers individually on behalf of their patients, less than half of the centres which replied to the survey provided specific written guidance for teachers about schooling for children with cancer. All the written material available provided the same overview of cancer in children, its frequency and treatment, and stressed the importance to the child of an early return to school. Only a few, however, addressed issues such as an explanation that children are usually aware of their diagnosis and that acute medical problems occurring in children while at school are unlikely—both areas that would provide considerable reassurance for teachers' anxieties. The provision of teaching in hospital, the use of the home teaching service and part time attendance at school are all ways in which schooling can be continued until the child is well enough to return to a full time curriculum—points discussed by some leaflets only. It is interesting that all leaflets countered the anxiety that cancer might be infectious and emphasised that the affected child presents no risk to others—a reassurance that many might be surprised to believe is necessary.

The problems experienced by children with cancer, and their teachers, are not unique and some of the solutions might apply equally to children with other medical problems (for example, cystic fibrosis and diabetes). The relation between medical services and schools has recently been considered by the British Paediatric Association and the need for interprofession liaison was emphasised.[10] The value of educational programmes, including seminars and meetings, as well as the provision of written information, in educating teachers and school medical nursing staff about the problems of school for the child with cancer has been established.[11] Certainly, the introduction of meetings for teachers of recently diagnosed children in our own unit has been received with enthusiasm. Whether such efforts have appreciably improved the excessive absenteeism and educational disruption seen among this group of patients remains unproved How such an improvement can be best achieved must be the focus of further study.

We thank our colleagues in the other regional paediatric oncology centres for their help in undertaking this study

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Archives of Disease in Childhood, 1988, **63**, 459–462

Correspondence

Sexual abuse in children

Sir,

For many years the nature of my outpatient clinical caseload has necessitated careful inspection of the anus and genitalia in some three quarters of new attenders and many of those recalled for review. Am I now to believe, following the claim in the article by Drs Hobbs and Wynne that up to one in three children are sexually abused,[1] making it some five times as common as urinary tract infection, and that I have missed several cases a year?

These authors, as well as Dr Leventhal and colleagues,[2] imply that abuse needs to be suspected in children complaining of enuresis, vaginal discharge, and abdominal pain These are common organic symptoms in childhood and only occasionally have a psychosomatic basis. Most daytime wetting in girls is due to the urge syndrome; sitting in damp pants causes non-specific vulvitis, with or without discharge, and ammoniacal dermatitis of the labial skin that sometimes extends to the perianal region. The associated pain or itching, or both, may lead to scratching and to digital manipulation of the introitus by the child herself. How may this affect the appearance of the vulva and hymenal diameter? Vaginal sleeve swabs almost invariably grow commensals and, in 22 years' paediatric practice I have only once cultured a sexually transmitted organism; this was in an adolescent girl who admitted having intercourse voluntarily, outside her family circle

Most girls with urge incontinence have disguised constipation, the clue to which is a firmly palpable descending colon· they sometimes also complain of recurrent abdominal pain, centrally or in the left flank Dietary enquiry often reveals fibre deficiency, and correction not only eliminates the abdominal pain but also improves the wetting.[3] Observations on these girls has led me to recognise that most children of either sex complaining of recurrent abdominal pain have a similar problem of dietary fibre deficiency and are not emotionally disturbed. The passage of large, hard stools undoubtedly inflicts damage on the anus, as recently reported [4] The anal reflex, elicited routinely to test the integrity of sacral innervation in incontinent children, requires that a relaxed anus contracts in response to stimulating the perianal skin. How easy it would be for the inexperienced to interpret the preliminary relaxation as 'reflex dilatation' and the reflex contraction as 'twitchiness '

While I do not doubt the existence of sexual abuse, or the sincerity of Drs Hobbs and Wynne, I am disturbed by the distortion of perspectives which their article creates. In the real world, parents need to have confidence that the paediatrician to whom they take their child for advice can be trusted to deal sympathetically with their symptoms, be they enuresis or abdominal pain, and not subject them to an inquisition with sexual abuse uppermost in his or her mind. In their final comments (p 1195) Drs Hobbs and Wynne imply that the current controversy has polarised paediatricians and police surgeons. If, indeed, it is a contest, I would suggest that it is the police surgeons who are making the paediatricians look foolish!

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Sir,

The highly publicised controversy concerning the significance of anal dilatation has produced a series of dogmatic assertions that have already been influential in the collapse of care proceedings in a number of cases It is high time their logic was challenged.

Dr Raine Roberts, writing in this journal, states that anal dilatation in a 'subjective and misleading test '[1] Her distrust of anal dilatation seems to be based on two arguments: firstly, she states that she and her colleagues in Manchester, seeing children for police and social services, have found anal signs in only a handful of cases compared with the large numbers described in Leeds.[2] Dr Wynne supports her cases with photographs and detailed case histories Surely Dr Roberts is not suggesting that Dr Wynne has fabricated her results? Secondly, she states that anal dilatation 'cannot be used in evidence. because it is also present in some children who have not been abused.' She states that dilatation can occur in constipation, threadworm, and anal thrush She supports this statement with reference to Dr Graham Clayden in a letter to the *Lancet*.[3] Dr Clayden's letter makes no mention of thrush or threadworm and simply states his belief, based on experience with a highly specialised clinic population, that chronic constipation can cause anal dilatation He produces no numerical data, however, and appears to make the assumption that those children manifesting anal dilatation are not silent victims of sexual abuse, without undertaking any investigation or disclosure work.

A multitude of possible causes of anal dilatation have been named in courts of law and in the media, but in fact no study exists that shows or even suggests the occurrence of anal dilatation in association with such conditions as thrush, threadworm, diarrhoea, or indeed, constipation Moreover all these speculated causes are commonplace in childhood whereas anal dilatation is very rarely seen in normal clinical practice. The only circumstances where anal dilatation has been documented is where anal abuse has occurred. Dr Wynne presented her data in a scholarly and thorough manner which clearly shows a strong association between the finding of anal dilatation and the disclosure of anal abuse Our experience in Newcastle has been very similar.[4]

There is a pressing need for studies of anal findings in normal and encoporetic children to clarify this difficult area. In the meantime we must firmly resist the acceptance of dogmatic statements that are unsupported by objective data.

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Child abuse—consequences for health services

SIR,

During the course of a study on the work pattern of health visitors we have observed the effect the rise in the number of cases conferences (table) for child abuse has had on their work. The notification and follow up of possible child abuse takes precedence over all else Some health visitors in this district are finding their attendance at case conferences is ranging from once a week to daily Moreover each child placed on the register is made the subject of extra visiting, often requiring as many as three additional weekly visits Each newly registered case of child abuse can add anything from two to 12 hours to a health visitor's weekly workload, depending on its complexity A senior health visitor estimated that four hours represented either 24 hearing tests, seeing 20 mothers and babies in a clinic, or six home visits. The very small amount of visiting to other important 'at risk' groups, such as the elderly, is further eroded. Only the effect on the work of health visitors has been directly observed but this is paralleled by similar effects on the work of general practitioners, child psychiatrists, paediatricians, and social workers, as many as 10 or more of whom may be involved in a case conference [1] Staff shortages in social work departments and in the health visitors establishment are compounding the problem

Table Data from Tower Hamlets Youth and Community Section

Year	*All case conferences*	*New case conferences*
1980	100	78
1981	251	89
1982	299	91
1983	304	89
1984	335	90
1985	435	131
1986	566	190

Provided by Youth and Community Section Metropolitan Police Tower Hamlets

Insufficient cognisance is being taken of the cost for clients and professionals of the disruption to planned health programmes because of the crisis imperatives of child abuse and in particular the time devoted to attendance at case conferences. It has already been pointed out that little attempt has been made to evaluate their effectiveness [2]

In consultation with other agencies every district should look anew at the number of professionals involved in case conferences and their particular contribution This would allow 'agencies to place more emphasis on the earlier provision of services to children and families who need help' as recommended by the DHSS [3]

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Validity of forced expiratory flow volume loops in neonates

SIR,

We are concerned that the methodology described in the paper of Hoskyns *et al* regarding the forced expiratory flow volume technique used in infants is flawed and that the conclusions reached by the authors may be misleading [1]

Our first concern is that these workers have not provided evidence that maximal expiratory flow was achieved in the infants they studied They used a single narrow range of compression pressures and did not evaluate the transmission of pressure from the jacket to the pleural space in each subject We have recently reported that a single jacket pressure will not reliably achieve maximal expiratory flow in all infants, as the transmission of pressure varies between different jackets and between different infants.[2] Thus a wide range of jacket pressures must be used in each infant to ensure that maximal flow is obtained [2] The high mean coefficient of variation (CV) for maximum flow at functional residual capacity (VmaxFRC) of 19·7% (calculated from table 1) suggests that the methodology used by Hoskyns *et al* was not reliable

Much of the data reported by the Nottingham group relates to 'squeezes applied at different points in the respiratory cycle ' The relevance of their observations relating to these 'mistimed' squeezes is obscure as the need for accurate timing of the squeeze at end-inspiration has been consistently stressed,[2–4] and acceptable CVs for VmaxFRC (mean CV 9·5%[3] and 11%[4]) have been obtained using accurately timed end-inspiratory squeezes

The authors claim that inspiratory muscle activity 'may interfere with measurement of airway function' but provide no data with correctly timed squeezes to substantiate this claim. Figure 5 does not support their assertions as inspiratory muscle activity has not affected VmaxFRC: oesophageal pressure does not fall until *after* expiration has passed FRC If inspiratory muscle activity does occur before FRC is reached, the problem can be simply solved by using a higher compression pressure [2]

We would also like to point out that the 'supramaximal' flows for squeezes applied during expiration are likely to be caused by flow transients from compression of gas in large airways If an adequate compression is used from end-inspiration and appropriate care is taken to ensure that expiration is flow-limited, additional compression force will not increase expiratory flow [2]

Critical evaluations of new techniques are to be welcomed, but such evaluations must themselves be methodologically sound

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The colour of light for neonatal phototherapy

Sir,

In a recent paper by Ayyash *et al* comparing green and blue light for the phototherapy of neonatal jaundice the summary stated 'A total of 262 neonates were treated with green (350–650 nm) or blue (300–600 nm) light . . . .'[1] We feel this statement is not only incorrect but potentially hazardous.

Firstly, the spectral ranges quoted by the authors are puzzling as green light is normally accepted to lie within the wavelengths interval 500–570 nm, and blue light within 440–500 nm [2] More importantly, the statement that the

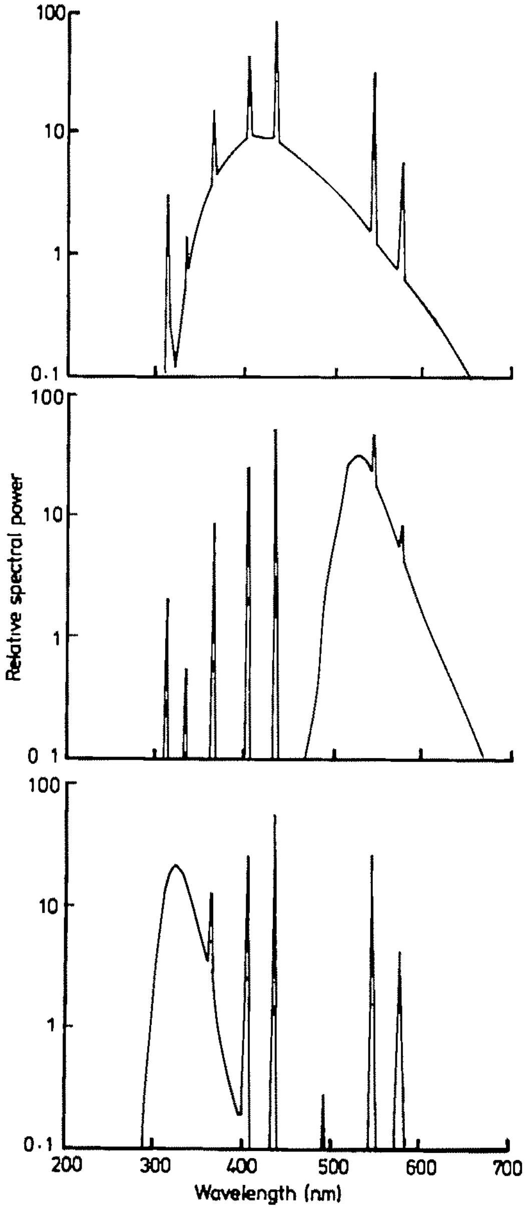

Figure *The relative spectral power distribution from a Sylvania F20T12B (blue) lamp (top), T20T12G (green) lamp (middle), and Wolff Helarium (ultraviolet) lamp (bottom)* spectral emission lies between 300–600 nm for the blue lamp, with the implication that it is this spectral interval which is required for effective phototherapy is misleading. The spectral emissions of the Sylvania F20T12G (green) and F20T12B (blue) lamps used by these authors are compared here with the spectral emission of another lamp which is also frequently available in hospitals, an ultraviolet lamp used for the phototherapy of psoriasis (figure). A potential source of confusion is that nearly all ultraviolet fluorescent lamps emit a pale blue light not dissimilar from the blue fluorescent lamps used for neonatal phototherapy The statement that the spectral emission lies between 300 to 600 nm could equally be made for each of the lamps. Yet if neonates were exposed to the radiation from an ultraviolet fluorescent lamp for the same time that they are normally exposed to 'blue light' the resulting erythema would be severe and possibly fatal.

Although it could be argued from the figure that the spectral emission of the blue light does lie between 300–600 nm, a statement like this is meaningless unless it is qualified by reference to the biological action of the radiation, as all photobiological phenomena, such as erythema, bilirubin dissociation, or photosynthesis show a strong, but different, dependence on the wavelength of the radiation.

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When not to do a lumbar puncture

Sir,

Dr Addy, writing of meningitis, says that he will consider treatment without lumbar puncture when a child 'has fundoscopic evidence of raised intracranial pressure '[1] He may not intend the implication, but to many his statement will imply that optic disc swelling is a feature of increased intracranial pressure in acute illness Although it is well recognised that papilloedema is commonly present when chronic or subacute conditions (tumour, abscess, lead encephalopathy, etc) present acutely, it must be exceedingly rare in acute pyogenic meningitis or indeed other short duration illnesses with brain swelling and high intracranial pressure

This does not mean that fundoscopy should be neglected Retinal haemorrhages may be prominent in meningococcal septicaemia in the absence of any purpuric skin rash We have seen two such cases In one, the diagnosis was delayed because non-accidental injury was wrongly suspected. In the other, a combative child with diarrhoea and vomiting, retinal haemorrhages were not recognised until after lumbar puncture and intravenous fluids, and fatal brain swelling ensued

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Dr Addy comments

I accept that papilloedema must be rare in acute meningitis. In the typescript of my annotation I wrote 'fundal signs of raised pressure are not to be relied upon.' This was changed in the published version to 'fundal signs of raised pressure alone are not adequate ' The message remains the same.

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Book reviews

Pediatric and Fundamental Electrocardiography. Edited by Jerome Liebman, Robert Plonsey, and Yoram Rudy. Pp 406. £78 hardback. Martinus Nijhoff Publishing, 1987. ISBN 0-89838-815-5.

This multiauthored book may be divided into three parts The first deals with topics in basic science electrocardiography, the second with arrhythmias and electrophysiological techniques in children, and the third with body surface potential mapping Hence the unusual, and somewhat unnatural, combination of 'Pediatric' and 'Fundamental' electrocardiography of the title It is hard to envisage a wide audience for this selected combination of topics. The basic science sections require knowledge in physics beyond the scope of most clinicians While some of the clinically based chapters are well written and comprehensive, coverage of the field is very uneven For example, there are no guidelines as to what constitutes a 'dangerous' accessory pathway in Wolff Parkinson White syndrome, despite the major emphasis on electrophysiology The book is well presented, with excellent reproduction of electrocardiograms and electrophysiological data. It is unlikely to be of major interest to paediatricians, however, and its appeal would seem confined to the small number of paediatric cardiologists with an electrophysiology interest, and the even smaller number of basic scientists in this field.

I SULLIVAN

Drug Therapy for Asthma: Research and Clinical Practice (Lung Biology in Health and Disease Series Vol 31). Edited by John W Jenne and Shirley Murphy. Pp 1152: $169·75 (US and Canada) $203 50 (all other countries) hardback Dekker, 1987 ISBN 0-8247-7633-X.

This is one of those increasingly popular multiauthor books dealing with all aspects of drug treatment in asthma. Most of the 41 contributors are North American and the book forms the 31st volume in the series *Lung Biology in Health and Disease.* The editors claim the book provides in one source both the 'theoretical groundwork and practice specifics of asthma drug therapy.' The small print does not make the book easy to read but much information is included on all aspects of drug treatment of asthma: smooth muscle anatomy, airway receptors, calcium channel blockers, and in vitro studies of bronchodilators. Detailed studies on pharmacology and pharmokinetics of all drugs are described; some of these are no longer in clinical use in the United Kingdom Two interesting chapters compare the clinical management of adult asthma both in the United Kingdom and the United States American experience with methyl xanthines is described at length. There is a useful chapter on aerosol dynamics and delivery systems

Both paediatric chapters give a good account of North American practice The difficulties using theophyllines are again emphasised with newer methods of monitoring. Topically active steroids have only one paragraph with two recent American references. Dry powder inhaled steroids are not mentioned Salbutamol respirator solution only became available last year in the United States.

The British paediatrician will find little to help with clinical practice in this country. This is an expensive book for the paediatric department bookshelf. Nevertheless, it is a comprehensive well referenced work useful for all those actively involved in asthma research

J COGSWELL

Archives of Disease in Childhood, 1988, **63**, 464

British Paediatric Association

Training in community paediatrics

A seminar on training for community paediatrics arranged by the British Paediatric Association (BPA) and the Community Paediatric Group was held in July 1987.

Dr Marion Miles spoke on the subject of accreditation. Training programmes in community child health involve supervision as well as service experience. A number of approved posts at senior clinical medical officer grade have been established and others have been approved *ad hominem*. The number of posts is rapidly increasing and more are in the pipeline.

Professor Catherine Peckham described a new MSc course in community paediatrics that will start in 1988 at the Institute of Child Health in London. This course of three terms will include epidemiology, health economics and management as well as the more traditional areas of community paediatrics. Several similar courses are held at other centres and more are planned. These courses are designed to complement training programmes and will encourage the academic development of community paediatrics.

Dr Marion Crouchman outlined some of the difficulties facing newly appointed consultant paediatricians in community child health (CPCCH) who have often been inadequately trained for their complex managerial role and for the teaching and research aspects of their work. It is difficult to find time for administrative duties in addition to the heavy clinical workload.

Dr Simon Lenton discussed the results of a questionnaire submitted to those in training for community paediatrics. There was a wide variation in previous and current experience with most respondents having inadequate training in research, administration, and epidemiology. Estimates of the number of training posts needed to provide at least one CPCCH per district indicate the need for a large increase but the precise number will have to be accurately assessed from the results of the BPA manpower survey.

The Nottingham community training programme was described by Dr Leon Polnay. At senior house officer level trainees worked in parallel with an experienced supervisor. A day release course over three terms covered general paediatrics, handicap, and behaviour problems, and attachments to other services dealing with children were arranged. Training continued at registrar and senior registrar level and there was an overlap between those in short term training posts and senior doctors in permanent posts.

A joint training scheme between community child health and general practice in East Lothian was described by Dr Bill Basset. The general practice component of the training programme is supervised by general practitioners with a special interest in child health and is linked to the course at the Edinburgh School of Community Paediatrics which runs for a six month period.

Training in child development and handicap was discussed by Dr David Hall. He emphasised the importance of contributions from other disciplines such as neurology, child psychiatry, psychology, audiology, ophthalmology, and education.

It was concluded that considerable progress had been made in developing training programmes and that community child health was advancing in both academic and service areas. There is a need, however, for a further increase in the number of approved training posts and for training in epidemiology and administration to be included in existing posts. The Community Paediatric group agreed to collaborate with the BPA manpower committee in producing a realistic estimate of the number of training posts required.

A D M Jackson

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ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Clinical significance of IgA deficiency *Morgan and Levinsky* 579

Food additives *David* 582

Accidental poisoning *Craft* 584

Original articles

Clinical diagnosis of cryptorchidism *John Radcliffe Hospital Cryptochidism Study Group* 587

Sodium cromoglycate in asthma correlation between response and serum concentrations *Yahav, Dany, Katznelson, et al* 592

Severe hypoxaemia in pertussis *Southall, Thomas, and Lambert* 598

Age dependence of flow velocities in basal cerebral arteries *Bode and Wais* 606

Serological evaluation of a measles, mumps, and rubella vaccine *Robertson, Bennett, Jefferson, et al* 612

17OH-progesterone rhythms in congenital adrenal hyperplasia *Young, Robinson, Read, et al* 617

Androstenedione rhythms in saliva in congenital adrenal hyperplasia *Young, Walker, Riad-Fahmy, et al* 624

Growth hormone releasing hormone or growth hormone treatment in growth hormone insufficiency? *Smith and Brook* 629

Measuring severity of injuries to children from home accidents *Alwash and McCarthy* 635

Comparison of five tests used in diagnosis of neonatal bacteraemia *Kite, Millar, Gorham, et al* 639

Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome in three siblings *Elias, Horowitz, Tal, et al* 644

Sleep patterns of infants in the first year of life *Eaton-Evans and Dugdale* 647

Short reports

Radionuclide cystography in vesicoureteric reflux *Chapman, Chantler, Haycock, et al* 650

Feasibility of screening all neonates for hearing loss *Hall and Garner* 652

Campylobacter pylori gastritis *Mahony, Wyatt, and Littlewood* 654

Early sodium intake and later blood pressure in preterm infants *Lucas, Morley, Hudson, et al* 656

Silastic catheters for antibiotics in cystic fibrosis *Williams, Smith, Woods, et al* 658

Free amino acid content of the vitreous humour in cot deaths *Patrick and Logan* 660

Subcutaneous rheumatoid nodules *Mastboom, van der Staak, Festen, et al* 662

Relation between height velocity and fasting insulin concentrations *Hindmarsh, Matthews, Di Silvio, et al* 665

Prepubertal hypertrichosis. normal or abnormal? *Barth, Wilkinson, and Dawber* 666

Budd-Chiari syndrome treated by Senning operation *Mahony, Littlewood, Losowsky, et al* 669

Current topic

Prevention of mental handicap and developmental disabilities in South East Asia *Sardharwalla, Lingham, and Harvey* 672

Personal view

Community paediatrics: anxieties on future developments *Gordon* 674

Correspondence 678

Book reviews 686

British Paediatric Association 60 years

British Paediatric Association Annual Meeting 688

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Annotations

Clinical significance of IgA deficiency

IgA is one of the five classes of immunoglobulin found in biological fluids It is the major secretory immunoglobulin and is widely distributed in all mucosal secretions as a dimeric molecule linked by a joining chain and a third molecule, the secretory piece. The dimeric form is resistant to proteolytic digestion and IgA antibodies are important in the protection of mucous membranes against invasion by pathogens.[1] The function of serum IgA antibodies, which mainly exist in monomeric form, is unclear Low serum IgA, however, is a useful marker of secretory IgA deficiency which almost invariably accompanies it There is only one reported case of absent secretory IgA in the presence of normal serum IgA and this was associated with an absence of the secretory piece.[2] There are two serologically and structurally distinct IgA subclasses, IgA_1 comprises 90% of circulating IgA, but the IgA found in secretions is equally distributed between IgA_1 and IgA_2.[3]

IgA deficiency with normal concentrations of other immunoglobulin classes (isolated IgA deficiency) was the first[4] and is the most common immunoglobulin deficiency described The genetic basis of IgA deficiency is not known but there are associations with certain HLA-types, healthy IgA deficient individuals having an excess of HLA-B8 and DR3 and symptomatic ones an increased frequency of HLA-B40.[5] IgA deficiency usually occurs sporadically but is found with variable inheritance patterns within some families. The section of DNA coding for the α heavy chain of IgA within the immunoglobulin gene has always been found to be present in isolated IgA deficiency However no α chain messenger RNA was generated in polyclonally activated B-lymphocytes from IgA deficient individuals, making a DNA to RNA transcriptional defect possible in such patients.[6]

The incidence of IgA deficiency is approximately one in 500 of the general population.[1] Most of these individuals are healthy but a minority have significant symptoms. In these patients frequent upper and lower respiratory tract infections and middle ear infections predominate and in some significant organ damage such as bronchiectasis may result.[7] In subjects with allergic disorders and autoimmune diseases the incidence of IgA deficiency is higher, sometimes approaching one in 100.[1] Weak associations with IgA deficiency occur in coeliac disease, systemic lupus erythematosus and other autoimmune disorders,[1] gastrointestinal disease,[8] and some malignancies.[9] The dichotomy between symptomatic and asymptomatic IgA deficient individuals remains, however, often making the significance of the finding in individual patients unclear A further complication is the transience of IgA deficiency, both in adults[10] and particularly in children,[11] where it may represent delayed maturation of the humoral immune system. During ontogeny IgA is the latest of the immunoglobulin classes to develop, and normal serum and mucosal concentrations do not reach adult concentrations until puberty. Reversible IgA deficiency is also induced by some drugs including phenytoin.[12]

There are a number of possible explanations for the presence of symptoms in only a minority of individuals with isolated IgA deficiency.[13] The severity of the deficiency may be important as children with very low concentrations of IgA ($<0{\cdot}05$ g/l) had a higher incidence of pneumonia than those who were also IgA deficient but had concentrations $>0{\cdot}05$ g/l but < -2 SD below the mean for age. Furthermore, 50% of this latter group had only transient deficiencies but the more severe deficiencies were permanent.[10] Most even profoundly IgA deficient individuals are still asymptomatic, however, and in these subjects mechanisms which compensate for the lack of IgA are probably operating. One such mechanism may be the increased local production and passage of IgM into nasal secretions and saliva seen in asymptomatic but not symptomatic individuals [14] A third reason for the discrepancy of symptoms between individuals with isolated IgA deficiency may lie in variable associations with other covert immunodeficiencies. For example, low concentrations of certain subclasses of IgG, particularly IgG_2 and IgG_4, are found in approximately 15% of patients with IgA deficiency,[15] though in one study of 60 IgA deficient children this combination did not correlate with an increased incidence of infection.[16] Furthermore, qualitative[17] or quantitative[18] abnormalities in the IgG antibody response to infection or immunisation have been described even in the presence of normal or high total IgG and IgG subclass concentrations Pulmonary damage is more common in IgA deficient adults who have associated immunodeficiencies,[19] though it may also occur in IgA deficient individuals without demonstrable IgG abnormalities.

How then should the paediatrician, or more importantly the general practitioner, approach the child with isolated IgA deficiency? Asymptomatic individuals or those with very minima symptoms should be regarded as having a compensated immunodeficiency. Early recourse to antibiotics during intercurrent infections is justified, and vigilance should be maintained for evidence of organ damage, poor growth, or allergic symptoms. Their detection is an indication for careful assessment of middle ear and pulmonary status. In these subjects more detailed immunological investigations may be undertaken, but the initial approach is based on the clinical situation.

Associated allergic and other symptoms (autoimmunity, cough, sputum production, conjunctivitis, etc) should be controlled, and chest physiotherapy instituted, and middle ear drainage considered, especially if organ damage is evident. After this, a sequence of treatment should be followed until a satisfactory clinical response is obtained. The sequence consists of: (a) vigorous early antibiotic treatment during all infections; (b) prophylactic antibiotic treatment (once daily cotrimoxazole is useful in this context); and (c) intravenous immunoglobulin infusions.

Requirement for the second stage in this sequence should be preceded by further immunological investigation and before recourse to the third, assessment by a paediatric immunologist is desirable. Intravenous immunoglobulin should only be given if infections are severe or frequent enough to cause significant disability. They should be used with caution, as IgA deficient individuals occasionally have severe reactions to immunoglobin infusions caused by the development of antibodies to IgA.[20] Immunoglobulin preparations low in IgA may be preferable and monitoring for IgA antibodies is recommended.[20] Liver function tests should be measured regularly as non-A non-B hepatitis has, on rare occasions, been transmitted by some intravenous immunoglobulin preparations [21 22]

There are no accurate data on prognosis for symptomatic children, but there is a tendency to improve with age and probably at least 50% will not be symptomatic as older children or adults The IgA concentration may become normal in those with less severe deficiencies any time between six months after the first assessment up to the age of 14 years,[11] and on occasions thereafter.[10] Symptoms may improve despite persistence of the deficiency, presumably as the maturing immune system develops compensatory mechanisms. On rare occasions the converse may be true and IgA deficiency may precede the development of a more generalised hypogammaglobulinaemia. The discovery of IgA deficiency should alert the physician that he or she may be dealing with a patient with compromised immunity to infection. Patients should be monitored closely with a view to preventing the long term sequelae of IgA deficiency

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Archives of Disease in Childhood, 1988, **63**, 582–583

Food additives

I wonder how many people visiting a fishmonger realize that the colour of many fresh salmon is due to the presence of an artificially added colour. The flesh of wild salmon is pigmented with astaxanthin, which is obtained naturally from crustacea in their diet. Another colour, canthaxanthin, is added to the diet of farmed salmon to produce fish equivalent in colour to wild salmon.[1] Many people are probably also unaware that titanium dioxide is added at a concentration of up to 400 mg per kilogram to Mozzarella cheese made from cows' milk, in order to give this product the same white appearance as traditional Mozzarella cheese made from buffalo milk. The scale of use of additives in food comes as a surprise to most people and it is understandable that many should find these substances vaguely menacing.

Types of additives

Concern about food additives is not new In 1857, a survey of adulterants in food showed that childrens' sweets were commonly coloured by red lead (lead oxide), lead chromate, mercuric sulphide, and copper arsenite [2] But the current range of permitted food additives, and the scale of their use, is much greater than it was in those days. Food additives can now be classed as colouring agents, preservatives, antioxidants, emulsifiers, stabilisers, flavours, sequestrants, anticaking agents, acids, buffers, bases humectants, firming agents, crisping agents, thickeners, sweeteners, enzymes, and nutritive agents. Evidence linking most of these with disease states is lacking, but certain colouring agents and preservatives do have definite adverse affects in certain people. The substances most commonly blamed are azo dyes such as tartrazine, and preservatives such as benzoic acid and related compounds and the sulphites

Urticaria

Most accounts of urticaria provoked by food additives are technically unsound, but two good double blind placebo controlled studies have appeared.[3,4] Both were of patients with chronic urticaria, defined as lasting two months or more, who were attending allergy clinics, and who had responded to a diet avoiding colouring agents and preservatives. Tartrazine provoked attacks of urticaria in about a quarter of these patients. One of these studies showed that sunset yellow, amaranth, indigo carmine, sodium benzoate, sodium metabisulphite, and monosodium glutamate could also provoke urticaria in childhood.[3] It is reasonable to recommend that patients with chronic urticaria try a diet avoiding these additives, and doctors with a 'Sherlock Holmes' instinct can combine such a diet with a battery of double blind challenges so as to identify the causative substance.[3,5] The prognosis for additive induced urticaria in childhood seems to be good and in a recent study three quarters of a small group of children grew out of the problem within one to five years.[6] What is as yet unclear is whether this spontaneous improvement represents a development of tolerance towards the additive or a loss of the urticarial state. The latter is more likely, as it has been shown that urticarial reactions to tartrazine and salicylates mainly occur when the disease itself is active.[7]

Asthma and atopic eczema

It is a common though poorly documented observation that orange squash, lemon and barley water, and similar drinks which rely heavily for their appearance and flavour upon artificial ingredients, can precipitate coughing and wheezing in some children with asthma It is not always easy to unravel the causative ingredient, for these reactions can be caused by tartrazine,[8] sodium benzoate,[9] cola,[10] and probably most common of all, sulphur dioxide.[9] The cold temperature of the drink can also be responsible.[10] I would estimate that in addition, based on unpublished observations of 500 children with severe atopic eczema, the ingestion of tartrazine or benzoic acid may exacerbate the skin lesions in at least 5% of all children with atopic eczema. It is unclear whether additives aggravate eczema by producing urticaria, which seems the most likely explanation, or whether they are directly capable of worsening eczema.

Mechanism

The mechanism of action of additives such as tartrazine in triggering urticaria or atopic disease is uncertain. Most evidence suggests that the action is pharmacological rather than immunological,[11] and a recently published study showed rises in plasma histamine concentrations after ingestion of 200 mg tartrazine.[12] It is unclear whether the findings in this study of normal subjects, which employed doses of tartrazine well above the average daily intake, necessarily explain the mechanism of action of smaller quantities in the clinical situation

Behaviour

The avoidance of additives seems to have only a very short lived beneficial effect on behaviour problems, and both hospital[13] and community based[14] double blind studies have repeatedly failed to show any validity in the idea that additives cause behavioural problems in otherwise healthy people. A major source of confusion has been the presence of atopic disease. If an additive makes eczema or asthma worse, the concentration span and behaviour may also be expected to suffer, but there is no evidence that this is anything other than an indirect effect.

Public misinformation

The passion for food that is natural is not new. By the late 1850's, 'pure and unadulterated' had become the stock advertising slogan of those anxious to cash in on the then newly awakened fears of the public.[2] The recent obsession with natural food ignores the wide range of naturally occurring toxins. Examples are oxalic acid in rhubarb; goitrogens in brassicas; cyanogens in almonds, tapioca, and lima beans; 5-hydroxy tryptamine in bananas; psoralens in celery, peas, and parsley; solanine in potatoes; myristicin in nutmeg and carrots; and lectins in red kidney beans.[15] The concept of a 'health food' shop is misleading. For example, a recent survey of 'crunchy' peanut butter showed that 11 out of 59 samples from health food producers contained over 100 μg/kg of aflatoxins, over 10 times the proposed maximum permitted level for total aflatoxins.[16] Only one of the 26 samples from other producers contained aflatoxins in excess of 10 μg/kg, and none contained more than 50 μg/kg.

Food arouses not only the appetite but also the emotions. Current misinformation is attributable to numerous alarmist books, uncritical coverage by the media, and misguided advice by health care professionals. The avoidance of all foods containing additives, regardless of the fact that some are naturally occurring substances such as ascorbic acid, is widespread but illogical. There is an understandable desire of parents to focus the blame on a chemical rather than to face up to other causes for their child's bad behaviour or to the fact that the cause is not known. At present the major problem with food additives is the level of public misinformation about the subject, which often leads to inappropriate and occasionally handicapping dietary restriction.[17]

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Accidental poisoning

When most of us write a prescription we are thinking of the appropriate medicine for our patient and the type of packaging in which it is dispensed concerns us little. Since 1975 the way in which medicines have been dispensed has changed. Child resistant containers were first introduced for aspirin and paracetamol. After a dramatic reduction in the numbers of children admitted with (in particular) salicylate poisoning, an agreement was reached, in 1981, between the pharmaceutical and medical professions that all solid dose medicines should be dispersed with either a reclosable child resistant container or in unit packaging of strip or blister type. Although the impact on hospital practice of the introduction of these containers for salicylates was dramatic with an 85% fall in admissions from 1975 to 1978,[1] recent years have seen little apparent change in the pattern of poisonings admitted. If child resistant containers are apparently so effective for salicylate why hasn't there been the same success for other medicines since 1981? The two main reasons for this are that there has been considerably less than universal implementation of the 1981 agreement which was not regulation, and that no effective child resistant container exists which can be put onto a standard medicine bottle containing liquid medicine. Most liquid medicines are supplied to pharmacists in bulk and have to be decanted into smaller bottles. The lack of compliance with the 1981 agreement is due to the considerable opposition of the medical and pharmaceutical profession. Many feel that they are not effective and others that most poisoning episodes are so trivial as to be not worth preventing.

Although childhood poisoning is thankfully now a rare cause of death with only five deaths in 1985, it accounted for over 25 000 admissions to hospital in England and Wales in 1984. Many of the children admitted have no symptoms and are simply observed overnight, yet considerable disruption is caused to the child and his family. Before the advent of child resistant containers attempts at prevention had been primarily educational with little noticeable effect. In order to clarify the situation with regard to childhood poisoning a multicentre study was set up coordinated by the National Poisons Information Service (NPIS). Its aims were not only to look at the causes of accidental poisoning and their outcome but also to investigate the role of the type of packaging. It was hoped that this might give information on the effectiveness of child resistant containers compared with conventional packaging and in addition provide information on the relative safety of different forms of child resistant container concerned

One of the problems with such studies is that where only admissions to hospital are looked at it is impossible to interpret the relative contribution of different types of packaging unless 'exposure' data is also available A parallel survey was therefore carried out to determine the availability of medicines in the homes of children in the same study areas as used for the poisoning study. The results of these studies have recently been published.[2] [3] An additional stimulus for this study was the move towards unit dose and original pack dispensing—that is, the drug is manufactured with a 'course' of medicine in a single pack which can then be dispensed as such without the pharmacist having to count out tablets or decant into smaller bottles. It is considered that the advantages to patients outweigh the problems of the considerably increased amount of storage space required.

The poisoning study was undertaken in nine accident and emergency and five paediatric departments throughout England and Wales between 1982 and 1984. Altogether 2043 cases of poisoning were recorded in children under 5 years of age. Drugs accounted for 59%, household products 37%, and plants 3%. The most common drugs were analgesics, anxiolytics, cough medicines, and oral contraceptives; household products were usually bleach, detergent. disinfectant, and petroleum products. Seventy five per cent of the children were either 2 or 3 years old and there was a slight preponderance of boys (55%). Most drug incidents occurred between 9 am and 10 am and 75% were in the child's own home. Seventy six per cent of incidents happened when the child was not closely supervised by an adult. Only 22% of the children were admitted for observation and most required only emesis with ipecacuanha or fluids, or both. Seven children were admitted to an intensive treatment unit and there were no deaths. This part of the study therefore provides an enormous amount of valuable information concerning the background to accidental poisoning. Comparison with other smaller surveys and with data from the Department of Trade and Industry's Home Accident Surveillance System suggests that the results are representative of the national scene.

In order to assess the role of packaging in the incidents concerning medicines the multicentre study results were compared with data from a household survey. The latter was carried out by experienced market research interviewers among a representative sample of households with children under 5 years of age The areas studied were within the catchment area of each hospital in the main study. The study was performed at three different times of year. Interviewers arrived at the house unannounced so that there was no opportunity to tidy up. Over 92% of houses visited willingly cooperated in the study and this compares very favourably with usual household surveys where an 85% positive response is regarded as excellent. Altogether 598 homes were visited and 5823 medicines, almost 10 per household, and their packaging were identified within them. The relation between availability of medicines within homes, the type of packaging used, and the medicines concerned in the poisoning episodes was assessed using an accident association index A low index indicated relative safety and a high index that that substance or type of packaging was more dangerous and therefore unsafe.

Despite the current recommendations most substances concerned in the poisoning episodes either were not in child resistant containers (63%) or were in transparent blister packs (20%). Both of these had a high accident association index. Child resistant containers, strips, sachets, and opaque blisters all had a low index. The accident association index of different medications was obviously complicated by the type of packaging concerned. Those substances which had a relatively high index on their own, however, were rendered much safer by the use of a child resistant container. Presciption medicines were more dangerous than over the counter substances and the former were more commonly concerned in incidents of poisoning. Investigation of the place of storage showed that only 40% of medications were in their normal storage place at the time of the accident. No pack had a low index when stored on an open accesible shelf indicating that both safe packaging and safe storage are necessary for safety.

What are the implications of these two studies for the future management of childhood poisoning? Clearly there are implications for the pharmaceutical and packaging industries. The study has shown that child resistant containers and opaque blister packs, strip packs, and sachets were less associated with poisoning episodes whereas transparent blister packs appeared to be more dangerous. As a result of the study the Proprietary Association of Great Britain have drawn up guidelines for the design of unit dose packs which exclude transparent blister packs. These guidelines have the backing of the Association of the British Pharmaceutical Industry. There is currently a strong move towards unit dose packaging and original pack dispensing for prescription medicines and this study will undoubtedly help to make future packaging safer for children. There are, as yet, however, no recognised standards for the production of non-reclosable packaging and no accepted test procedures for them as there are for child resistant containers. There are also no suitable child resistant containers designed for liquids and these accounted for 42% of the poisoning episodes in the NPIS study. There is a clear need to develop a child resistant container which will fit onto a standard liquid medicine bottle, although special child resistant containers have been developed for some over the counter liquid medicines—for example, Calpol.

There are also other measures that could help prevent poisonings. Currently medicine labels must bear the instruction 'Keep out of the reach of children.' It might be better to amend this to 'Keep all medicines locked up and out of sight of children.' The survey has shown that although medicines may appear to be out of the reach of children, if they are visible they will find a way of getting them. There is also a problem with liquid medicine kept in refrigerators where they are accessible to small children. Very few medicines actually need to be kept as cold as 4°C and the pharmaceutical industry is looking at stability and perhaps more appropriate labelling.

Undoubtedly most poisoning incidents are just scares and most children do not need to be admitted to hospital Is there any way that we can make inroads into the problem? For no matter how effective child resistant containers become some children will still be poisoned. Once a child has taken an apparent excess of a substance his parents will probably panic and even if they don't they still need medical advice as to whether or not the substance is potentially dangerous. The NPIS currently responds only to inquiries within the health and emergency services and is not directly accessible to parents. Some countries do have a service that is available to the public where they can obtain reassurance or appropriate advice regarding the seeking of medical attention. Such a service could substantially reduce the number of children attending hospital but would be unlikely to alter either the number of admissions or deaths. The availability of rapid reassurance, however, would be a great saving in family distress and to the burden on the emergency services. A working party has been established under the auspices of the Childhood Accident

Prevention Trust and the National Poisons Information Service to assess the feasibility of such a service for the United Kingdom A pilot scheme has been running in Leeds and after local publicity campaigns the public are now beginning to use it.

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Original articles

Clinical diagnosis of cryptorchidism

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SUMMARY We examined 3534 boys for cryptorchidism at birth, and, if present, again at 3 months of age. We compared Scorer's standard criterion for cryptorchidism, based on measurement of the testis from the pubic tubercle, with the simpler criterion of whether the testis was in the normal position, well down in the scrotum. At birth 210 (5·9%) boys were cryptorchid by measurement and 220 (6·2%) by position. By 3 months of age the cryptorchidism rate was identical (1·6%) whichever criterion was used. We therefore recommend that position be used as the sole criterion for diagnosing cryptorchidism. There was a clear decrease in the cryptorchidism rate with increasing birth weight. A testis that was undescended at birth was more likely to descend spontaneously by 3 months the lower its position along the normal pathway of descent. For a given position of the testis, cryptorchid babies weighing less than 2500 g had a greater chance of spontaneous descent by 3 months than larger babies. An independent effect of gestation is suggested; cryptorchid babies of less than 37 weeks' gestation were more likely to have normally descended testes at 3 months than babies of longer gestation.

The incidence of cryptorchidism in the United Kingdom has increased by more than 50% over the past two decades.[1-3] In the only two definitive surveys of the incidence of the condition[1 3] the diagnosis was based on measurement of the distance between the pubic tubercle and the centre of the testis as suggested by Scorer.[4] Using results from the first two years of a population based study in Oxford,[1] we show that a more practical and equally satisfactory definition of cryptorchidism can be based solely on the position of the testis without measurement. The same data are used to explore prognostic factors for spontaneous descent after birth.

Subjects and methods

All boys born between 1 November, 1984 and 31 October, 1986 in the John Radcliffe Hospital, Oxford, to mothers resident in a defined area around Oxford, were included in the study.[1] Before screening, permission to approach patients for the study was obtained from all general practitioners with patients in the study area.

In addition to the full examination by paediatric staff, each boy was examined for cryptorchidism during the first 24 hours of life by one of four specially trained research nurses. Boys admitted to the special care nursery were examined as soon after birth as their medical condition allowed. 'Non-white' babies and babies whose mothers either did not speak English or had a severe psychotic illness (two mothers) were not examined as part of this study The reason for this exclusion was that the mothers of these babies would not be eligible for the second stage of this study; an aetiological study of cryptorchidism necessitating a personal interview with the mother.

Altogether 3621 eligible boys were born alive in the 24 months of the study and we examined 3559 (98%) of them soon after birth. Seventeen mothers refused permission for their babies to be examined, 10 babies died, two very ill babies were transferred to specialist hospitals, and 33 left the hospital before being examined by the research nurse.

Of the 3559 boys examined at birth, 25 had major congenital malformations: Down's syndrome (one), Becker's multiple dystrophy (one), Freeman-Sheldon syndrome (one), gut malformations (six), heart defects (six), hydrocephalus (three), multiple dysmorphic features (five), and spina bifida (two). These boys were excluded from the study

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The mothers of boys cryptorchid at birth (see below) were asked before leaving hospital for permission to visit them at home when the baby was 3 months old; premature babies were visited three months after their expected date of delivery. At this visit the boy was re-examined; if one of his testes was still undescended, the boy was referred to a special paediatric surgical outpatient clinic to confirm the diagnosis. The reason that 3 months was chosen for the second examination is as follows: histological studies have suggested that spermatogonia counts in cryptorchid testes become abnormally low at some time between the age of 6 months and 2 years.[5] On the basis of this information and also the fact that psychologically the least damaging time for operation is either up to about 6 months of age or after the age of 3,[6] the decision was taken to perform orchidopexies as early as possible. Moreover, Scorer's data had suggested previously that most late descending testes do, in fact descend before 3 months of age.[3] The rationale for examination at three months after the expected date of delivery in premature infants is that these infants have a very high rate of cryptorchidism but many of the testes descend spontaneously. Although Scorer does not suggest that cryptorchid testes in premature babies descend after the third month,[3] his data are not strictly applicable to our series as very premature babies are now much more likely to survive.

In consultation with both paediatricians and paediatric surgeons we attempted to reproduce exactly the technique of examination and classification used by Scorer.[4] A testis was classified as cryptorchid if the centre of the testis was less than 4 cm below the pubic tubercle (2·5 cm at the birth examination for babies weighing under 2500 g). All measurements were rounded down to the nearest 0·5 cm. Measurement was made after manipulation of the testis into the lowest position along the pathway of normal anatomical descent without tension being applied. This definition of undescended testis is precisely that adopted by Scorer,[3] and, for the purposes of this paper defines 'undescended testis by measurement.' In addition to recording these measurements of the testes, the position of each testis was classified as follows: normal (well down in the scrotum), high scrotal, suprascrotal (palpable, in the line of normal descent including the inguinal pouch, but not in the scrotum), non-palpable, and 'other'—ectopic (three), neonatal orchidopexy before examination (one), and position obscured by hernia or hydrocoele (two). This classification forms the basis of our definition of 'undescended testis by position', with all except testes well down in the scrotum being classified as undescended by this definition. Each boy was classified at birth according to his worst testis using each criterion separately. In only two boys out of the 3534 was the worst testis by one classification not the worst according to the alternative classification.

Statistical analysis was performed by the method of Mantel-Haenszel for testing the joint significance of differences in proportions in several two by two tables.[7] Tests for trend using the method of Mantel were stratified by birth weight if appropriate.[7]

Results

At birth 210 (5·9%) of the 3534 boys included in the study were found to have one or both testes undescended by measurement; there were 220 boys (6 2%) whose testes were undescended by position (table 1). There were nine boys whose testes were undescended by measurement but in a normal position, and 19 boys whose testes were normal according to measurement but positioned high in the scrotum or worse.

At 3 months of age 221 (97%) of the 229 boys who were born in the hospital and found to have an undescended testis at birth by either definition were re-examined. Of the remaining eight, one was inadvertently missed (he was examined at 11 months

Table 1 *Results of screening for cryptorchidism (November 1984–October 1986)*

Birth weight (g)	*No of boys examined at birth*	*Cryptorchid at birth*		*Cryptorchid at 3 months*
		By measurement	*By position*	
		No (Rate/100)	*No (Rate/100)*	*No (Rate/100)*
<2000	70	37 (52 9)	38 (54·3)	7 (10·0)
2000–2499	110	12 (10 9)	20 (18·2)	3 (2 73)
≥2500	3354	161 (4·8)	162 (4·8)	47 (1 40)
Total	3534	210 (5 9)	220 (6·2)	57 (1 61)

and found to have both testes descended), one moved out of the area, three withdrew consent for further examination, and three children were not examined because the mothers were considered emotionally unsuitable for inclusion (all were educationally subnormal). After consultation with the patient's general practitioner (or health visitor) all of these eight children were considered to have descended testes at 3 months and this has been accepted in this paper

Fifty seven of the boys we examined at 3 months of age were found to be cryptorchid; all of these boys were cryptorchid by both definitions. These 57 cases are shown by birth weight in table 1 The overall cryptorchidism rate had declined to 1·6% (57/3534)· 1·4% (47/3354) in boys weighing more than 2500 g at birth and 5·6% (10/180) in boys weighing less than 2500 g. These rates are very similar to our preliminary findings [1] At birth and at 3 months there is a clear decrease in the cryptorchidism rate with increasing birth weight (tests for trend, all have p<0·0001). This decrease continues with increasing birth weight into the highest birthweight group (greater than 4000 g) for the at-birth results, but not for the results at 3 months where there was no further decrease after 2500 g.

Table 2 shows the number of boys cryptorchid at 3 months and the number cryptorchid at birth cross classified by the measurement and position of the boy's worst testis at birth. All testes 4 cm or more from the pubic tubercle (or 2·5 cm or more for babies weighing less than 2500 g) descended spontaneously by 3 months of age. The nine testes classified as undescended by measurement at birth but in an apparently normal position well down in the scrotum were definitely descended at age 3 months. (In order to confirm the validity of Scorer's definition of normal descent in small babies as those having a measurement of more than 2·5 cm, we also re-examined 15 such babies whose worst testis was between 2·5 and 3·5 cm from the pubic tubercle at birth and in the normal position All were descended at 3 months.) As far as high scrotal testes are concerned, there is no evidence that measurement predicts descent: for babies weighing 2500 g or more at birth a slightly higher proportion of those with a more favourable measurement remained undescended Suprascrotal testes with a zero measurement (at or above the pubic tubercle), however, had less than half the chance of descending compared with those that had a non-zero measurement, although numbers are too small to show significance (two-sided p=0·18). Overall, suprascrotal testes with positive measurements do just as well as high scrotal testes. Testes that are not palpable or 'other' have a very high chance of remaining undescended at 3 months; 36 out of 57 (63%) of these had not descended spontaneously. There is a progressive increase in the proportion of undescended testes at birth that remain undescended at 3 months the worse the original position (two-sided p<0·0001). For a given position of the testis, babies weighing less than 2500 g appear to have a greater chance of spontaneous descent than larger babies (with the exception of the anomalous figure of six out of 51 for the larger babies with a suprascrotal testis that appears to be much too low).

Table 3 shows the number of boys cryptorchid at 3 months and the number cryptorchid at birth (by position) cross classified by gestational age and the position of the worst testis at birth We have distinguished between suprascrotal testes with a non-zero measurement and those at or above the pubic tubercle. The measurable suprascrotal testes are combined with those high in the scrotum. Babies cryptorchid at birth and with a gestational age of 36 weeks or less are more likely to have descended testes at 3 months than those with longer gestation;

Table 2 *Proportion of boys with undescended testis at birth whose testis was still undescended at 3 months (No undescended at 3 months/No undescended at birth (%)) by birth weight and measurement and position at birth*

Birth weight (g)	*Measurement of worst testis (cm)*	*Position of worst testis*					
		Normal	*High scrotal*	*Supra-scrotal*	*Not palpable*	*Other*	*Total*
<2500	0	-/-	-/-	5/19 (26)	2/5 (40)	1/2 (50)	8/26 (31)
	<2·5	0/4	1/11 (9)	1/8 (13)	-/-	0/0	2/23 (9)
	≥2·5	-/-	0/12	0/1	-/-	0/0	0/13
	Total	0/4	1/23 (4)	6/28 (21)	2/5 (40)	1/2 (50)	10/62 (16)
≥2500	0	-/-	-/-	4/20 (20)	30/46 (65)	2/3 (67)	36/69 (52)
	<2·5	0/0	1/12 (8)	2/26 (8)	-/-	1/1 (100)	4/39 (10)
	≥2·5–3·5	0/5	7/43 (16)	0/5	-/-	0/0	7/53 (13)
	≥4·0	-/-	0/6	-/-	-/-	0/0	0/6
	Total	0/5	8/61 (13)	6/51 (12)	30/46 (65)	3/4 (75)	47/167 (28)

Table 3 *Proportion of boys with undescended testes at birth whose testis was still undescended at 3 months (No undescended at 3 months/No undescended at birth (%)) by birth weight, gestational age, and position at birth*

Birth weight (g)	*Gestational age (weeks since last menstrual period)*	*Worst testis*				
		*Measurable**	*Not measurable†*	*Not palpable*	*Other*	*Total*
<2500	<36	1/21	2/15	2/4	1/2	6/42 (14)
	37–38	0/7	2/2	0/1	0/0	2/10 (20)
	≥39	1/4	1/2	0/0	0/0	2/5 (33)
	Total	2/32 (6)	5/19 (26)	2/5 (40)	1/2 (50)	10/58 (17)
≥2500	<36	0/7	0/1	0/1	0/0	0/9
	37–38	2/26	2/9	9/14	3/3	16/52 (31)
	≥39	8/59	2/10	21/31	0/1	31/101 (31)
	Total	10/92 (11)	4/20 (20)	30/45 (65)	3/4 (75)	47/162 (29)
All	Total	12/124 (10)	9/39 (23)	32/51 (63)	4/6 (67)	57/220 (26)

*High scrotal testes plus suprascrotal with non-zero measurement
†Suprascrotal testes with zero measurement

six out of 42 (14%) babies under 2500 g at birth and with a gestational age of less than 37 weeks were still cryptorchid at three months compared with four out of 16 (25%) of those with longer gestation. Among the larger babies, none with a gestational age of less than 37 weeks was still cryptorchid at 3 months compared with 31% of babies with gestational ages of 37 weeks or more (two-sided p=0·054).

We also compared those undescended testes which could be brought to a lower position under tension than that attained without tension, with those which could not be drawn down further under tension. There was no consistent difference in the proportions descending spontaneously between those that could be drawn to a lower position under tension and those that could not (data not shown).

Discussion

At birth 210 (5·9%) babies had an undescended testis by measurement, 220 (6·2%) by position, and 229 babies by one or both criteria. By the age of 3 months, however, all but 57 of these testes had descended spontaneously. None of the boys cryptorchid by only one criterion was cryptorchid at 3 months.

Although the research nurses working on this study have been trained together so that their interobserver disagreement in measurements is extremely low, in our experience other observers have considerable problems with these measurements. For this reason the use of precise measurements, except in a research project such as this, are unlikely to be reliable. As we have shown that equivalent results are obtained at 3 months whether measurement or position is used as the criterion for cryptorchidism and that the differences at birth are few, we would recommend that position is used as the criterion for defining cryptorchidism—namely, whether the testis is or is not well down in the scrotum.

The lower the testis along the path of normal descent at birth, the higher the chance that that testis will descend spontaneously by 3 months of age. In particular the two groups of testes that we have described as suprascrotal may be distinguished: those that are effectively at the pubic tubercle (that is, zero measurement) and those that are definitely below it. Those at the pubic tubercle have half the chance of those nearer the scrotum of descending spontaneously, and the latter group are as likely to descend as high scrotal testes. This justifies our amalgamation of these two groups in table 3.

The data shown in table 1 confirm Scorer's observation that the lower the birth weight, the higher the incidence of cryptorchidism.[4] This result holds even though we examined premature babies three months after their expected delivery date rather than according to their chronological age; this allowed extra time for the testes of these very small babies to descend spontaneously.

Although the numbers in this study are very small, an effect of gestational age in addition to birth weight is suggested by the results shown in table 3: the testes of cryptorchid babies of less than 37 weeks' gestation are more likely to descend by the age of 3 months than in babies of longer gestation.

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Sodium cromoglycate in asthma: correlation between response and serum concentrations

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SUMMARY The clinical response to sodium cromoglycate treatment was compared with its concentration in serum. Twenty five children with asthma entered a 10 week trial of two baseline weeks followed by eight weeks of treatment by the inhalation of 20 mg of sodium cromoglycate spincaps four times a day. Individual clinical response was determined by the differences between baseline and treatment periods of: (*a*) percentage of symptomless days (Δ score 0); (*b*) diary derived daily score for four symptoms (Δ DS); and (*c*) peak expiratory flow rate (Δ PEFR). At the end of the treatment period, patients inhaled a 20 mg spincap of sodium cromoglycate and the technique of inhalation was graded. Concentrations of sodium cromoglycate in serum were measured by radioimmunoassay in samples withdrawn 5 to 120 minutes after inhalation. Δ Score 0, Δ DS, and Δ PEFR correlated significantly with the area under the concentration time curve. Both the area under the sodium cromoglycate concentration time curve and clinical response correlated significantly with inhalation technique score. We suggest that response of children with asthma to inhalation treatment with sodium cromoglycate is correlated to its serum concentrations.

Sodium cromoglycate is an effective drug in the prophylactic treatment of asthma, especially in children. Its efficacy is ascribed to its ability to inhibit degranulation of mast cells in the respiratory tract.[1–4] It is claimed to be as effective as theophylline,[5 6] however, a quarter to a third of children appear not to respond to this treatment.[7 8] This failure could presumably be due to either a true non-responsiveness to the drug or inadequacy in its delivery to target site.

Using radioimmunoassay to measure sodium cromoglycate in normal volunteers it has been shown that concentrations in the blood are very low after oral ingestion.[9] Inhalation of the drug, however, led to much higher concentrations.[9 10] We report the results of a prospective study in which the clinical response was compared with concentrations of sodium cromoglycate in serum that were obtained after inhalation of the drug.

Patients and methods

Twenty five children with chronic perennial asthma participated in the study. There were 21 boys and four girls whose ages ranged from 7 to 14 years, with a mean (SD) of 10·4 (1·9) years. Duration of asthma ranged from one to 12 years, with a mean of 6·3 years. Criteria for inclusion were a history of moderate to severe asthma that was poorly controlled while on routine treatment, needing repeated visits to the emergency room and recurrent hospital admission during the year preceding entry. Patients had a personal or family history of associated atopic disorders and reversibility of airway obstruction as shown by improvement of at least 15% in forced expiratory volume in one second (FEV_1) 15 minutes after inhalation of 2·5 mg salbutamol. None of the children had received sodium cromoglycate previously, nor had they been treated with corticosteroids in the three preceding months.

The study was conducted over a period of 10 weeks. The first two weeks were a baseline period during which the patients were instructed in the inhalation technique of capsules of sodium cromoglycate by a powder inhaler, the spinhaler. The patients were instructed to use the inhaler after a forced expiration, to keep their lips tightly attached to the mouthpiece of the device, to take a deep forceful inspiration to inhale the powder and to hold their breath for 10 seconds afterwards. Salbutamol inhalation was permitted as necessary. Theophylline was stopped in those using it in order to assess better the effect of sodium cromoglycate as a single prophylactic agent and to exclude improved compliance to theophylline as a cause for the results obtained. Over the next eight weeks, the children inhaled 20 mg sodium cromoglycate spincaps four times a day while continuing to use salbutamol as needed.

The patients recorded the following symptoms in a daily diary on a 0–3 scale of increasing severity: sleep disturbance, cough, wheeze, and impairment of activity. Score 3 was given for each of the following symptoms: severe sleepless night, persistent cough, severe wheezes, and physical disability. Score 0 was given when the patient was asymptomatic. Daily score was determined for each day by the sum of the individual scores given to each symptom (maximum score=12) Twice daily the patients also measured peak expiratory flow rates (PEFR) at home, using a Mini-Wright peak-flow meter. Patients were assessed clinically at entry to the study and at the end of weeks two, six, and 10. During each assessment patients were examined, PEFR was recorded as described above, and FEV_1 was measured by a dry spirometer (Vitalograph). Patients were instructed to withhold the use of bronchodilators for at least 24 hours before their clinic visit On the fourth visit, the patients inhaled one 20 mg spincap of sodium cromoglycate. The technique of inhalation was assessed on a 0–3 scale taking into consideration strength and length of inspiration, motivation of performance, and positioning of patient's head and inhalation device. Venous blood samples for determination of sodium cromoglycate concentrations were drawn at 0, 5, 10, 30, 60, and 120 minutes after inhalation

Sodium cromoglycate concentration in the serum was determined by the radioimmunoassay method described by Brown *et al.*[11] Plots of the concentrations versus time were constructed, and area under the curve was calculated by the trapezoidal method.[12]

Response to treatment was assessed by three parameters: score 0, daily score (DS), and PEFR. The percentage of symptomless days recorded in the diary was calculated for the baseline period and for the eight treatment weeks, and was termed score 0. Mean daily score was calculated from the patients' diaries for both baseline and treatment periods. Mean PEFR was calculated for baseline and treatment periods. For each patient Δ score 0 and Δ DS were calculated as the differences between individual score 0, and mean daily score during baseline and treatment periods respectively. Δ PEFR was the difference between individual mean PEFR at treatment and baseline periods, divided by mean PEFR during baseline period and was expressed in per cent

Results were expressed as mean (SD) Means were compared by Student's *t* test, except for the comparison of means of daily score, where the Mann-Whitney test was used [13] A p value of less than 0·05 was considered significant.

Informed consent was obtained from the parents. The local hospital ethics committee approved the study.

Results

Table I shows clinical and pharmacokinetic data of the patients. Treatment with sodium cromoglycate produced no side effects Mean (SD) score 0 in the baseline period was 19·8 (23·3)% and in the treatment period 59·8 (32·3)% similar to the value obtained by Newth *et al.*[14] The rise in mean score 0 during treatment is significant ($p<0·002$). There was no difference in mean score 0 after four or eight weeks of treatment Mean daily score during the baseline and treatment periods, was 2·64 (1·1) and 0·85 (1·1) respectively ($p<0·001$). Cough and wheeze were the two symptoms which contributed most to the calculated daily score. Mean PEFR during the baseline period was 260 (61) l/minute and during treatment, 307 (76) l/minute ($p<0·02$) FEV_1, which was measured only during the clinic visits, was 69·3 (15·5)% on admission to the trial, 78·6 (19 5)% at the end of the baseline period, and 89·5 (18·2)% at the end of the trial.

Serum sodium cromoglycate concentration determined after inhalation of 20 mg of the drug rose rapidly. In 11 patients it reached a peak five minutes after inhalation, in eight patients 10 minutes after inhalation, and in five patients 15 minutes after inhalation. Peak concentrations varied considerably among the patients (table I). Mean peak sodium cromoglycate concentration was 51 µg/l, and the mean value 120 minutes after inhalation was 13 µg/l. The area under the sodium cromoglycate concentration time curve was calculated for each patient. Individual clinical response measured as the parameters Δ score 0, Δ DS, and Δ PEFR were correlated with the pharmacokinetic parameters: area under the curve, peak sodium cromoglycate concentration, and the clinically convenient parameter of sodium cromoglycate concentration 10 minutes after inhalation (SCG 10 minute)

Table 2 shows that the correlation between Δ score 0 as well as Δ PEFR and all the pharmacokinetic parameters was significant, Δ DS corre-

Table 1 *Clinical and pharmacokinetic data of patients*

Patient No	*Sex/Age (years)*	*Weight (kg)*	*Height (cm)*	*Severity of asthma*	*Medications**	*Δ Score 0†* (%)	*Δ DS‡*	*Δ PEFR§* (%)	*Technique score*	*Area under the curve (µg/l×hour)*	*Sodium cromoglycate concentration (µg/l)*	
											Peak	*SCG 10 minute*
1	M/12	[illegible]	128	Moderate	Salbutamol	88	1·4	16	3	79	90	74
2	M/10	27	133	Moderate	Salbutamol, theophylline	36	1·6	16	3	116	68	53
3	M/8	34	134	Moderate-severe	Salbutamol, theophylline	5	−1·0	−19	1	11	13	12
4	M/9	[illegible]	137	Severe	Salbutamol corticosteroids	16	2·2	11	1	22·5	15	15
5	M/10	[illegible]	126	Severe	Salbutamol, theophylline, corticosteroids	81	4·2	47	3	101	63	63
6	M/10	[illegible]	135	Moderate	Theophylline	60	2·3	9	2	57·5	71	71
7	M/14	35	160	Moderate	Salbutamol, theophylline	6	1·2	50	2	46	66	24
8	M/10	35	140	Moderate-severe	Salbutamol, theophylline	0	1·5	7	0	7·5	10	7
9	F9	39	135	Moderate-severe	Salbutamol, theophylline, corticosteroids	21	1·3	−7	2	37	52	35
10	M/14	45	160	Moderate-severe	Salbutamol, theophylline, corticosteroids	74	2	19	1	25	18	15
11	M/7	25	126	Moderate	Salbutamol, theophylline	52	0·35	11	2	26·5	21	21
12	M/9	30	134	Moderate-severe	Salbutamol, theophylline	27	0·7	26	2	58·5	50	50
13	F/11	28	127	Moderate	Salbutamol	25	1·5	9	2	46	54	42
14	M/13	46	165	Severe	Salbutamol, theophylline	0	2·75	2	1	32·5	18	13
15	M/9	30	132	Severe	Salbutamol, theophylline, corticosteroids	38	1·75	21	2	60	50	50
16	F/12	42	153	Moderate-severe	Salbutamol, corticosteroids	13	0·3	21	1	36·5	45	45
17	M/12	32	141	Moderate-severe	Salbutamol, theophylline, corticosteroids	33	1·35	6	0	21·5	30	28
18	F/8	36	138	Moderate	Salbutamol, theophylline	44	1·5	7	2	43·5	58	58
19	M/10	40	148	Moderate	Salbutamol	50	2·5	25	3	91·5	105	101
20	M/9	23	137	Severe	Salbutamol, theophylline, corticosteroids	49	4·1	25	2	36·5	61	40
21	M/10	33	145	Moderate-severe	Salbutamol, theophylline	77	2	17	3	85	108	103
22	M/12	40	154	Moderate	Salbutamol	9	0	40	1	40	53	53
23	M/9	23	125	Severe	Salbutamol, theophylline, corticosteroids	74	4	24	3	62·5	59	33
24	M/9	31	137	Severe	Salbutamol, corticosteroids	80	2·7	75	3		68	68
25	M/14	33	142	Moderate	Salbutamol	46	1·5	7	3	35	27	27

*Medications taken in the 12 months before sodium cromoglycate.
†Δ Score 0=difference in percentage of symptomless days between baseline and treatment period, ‡Δ DS=difference in mean diary derived daily score for four symptoms between baseline and treatment period; §Δ PEFR=difference in mean peak expiratory flow rate between treatment and baseline period

Table 2 *Correlations between clinical and pharmacokinetic parameters*

		r Value	*p Value*	*No of patients*
Δ Score 0*	*v* area under the curve	0·525	<0·005	24
Δ Score 0	*v* peak concentration of sodium cromoglycate	0·527	<0·005	25
Δ Score 0	*v* SCG 10 minute	0·561	<0·005	25
Δ DS†	*v* area under the curve	0·339	<0·035	24
Δ DS	*v* peak concentration of sodium cromoglycate	0·281	<0·08	25
Δ DS	*v* SCG 10 minute	0·226	>0·10	25
Δ PEFR‡	*v* area under the curve	0·455	<0·015	24
Δ PEFR	*v* peak concentration of sodium cromoglycate	0·451	<0·02	25
Δ PEFR	*v* SCG 10 minute	0·401	<0·04	25

*Δ Score 0=difference in percentage of symptomless days between baseline and treatment period; †Δ DS=difference in mean diary derived daily score for four symptoms between baseline and treatment period; ‡Δ PEFR=difference in mean peak expiratory flow rate between treatment and baseline period

lated significantly only with the area under the curve. The correlation between Δ score 0 and SCG 10 minute is shown in fig 1 and the correlation between Δ PEFR and area under the curve is shown in fig 2.

In order to determine whether the technique of inhalation of sodium cromoglycate affects clinical response to the drug, the pharmacokinetic parameters and clinical response were correlated with the efficiency of the technique of inhalation. Table 3 shows that highly significant correlations were obtained between the area under the curve, peak concentration of sodium cromoglycate, and SCG 10 minutes, and technique of inhalation. The correlation between the area under the curve and technique of inhalation is shown in fig 3. There is also a correlation between clinical response and inhalation technique, but its significance is smaller (table 3).

Finally, in an attempt to assess the effect of improved delivery of sodium cromoglycate, four patients with low peak sodium cromoglycate concentration were reinstructed in the use of the inhaler. In three patients peak concentrations rose from 29 (10) µg/l to 64 (15) µg/l ($p<0·025$). In one patient it did not change.

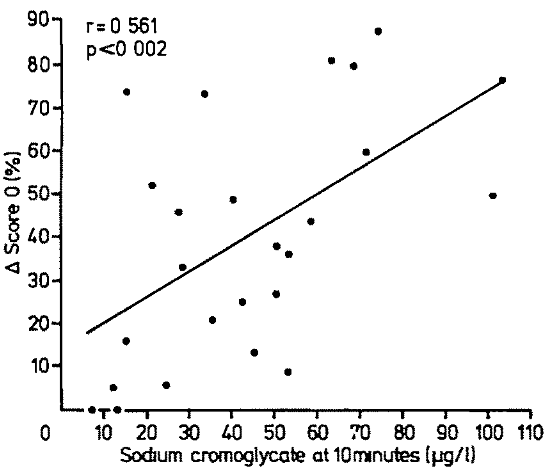

Fig 1 *Correlation between the difference in percentage of symptomless days during baseline and treatment period (Δ score 0) and concentration of sodium cromoglycate at 10 minutes.*

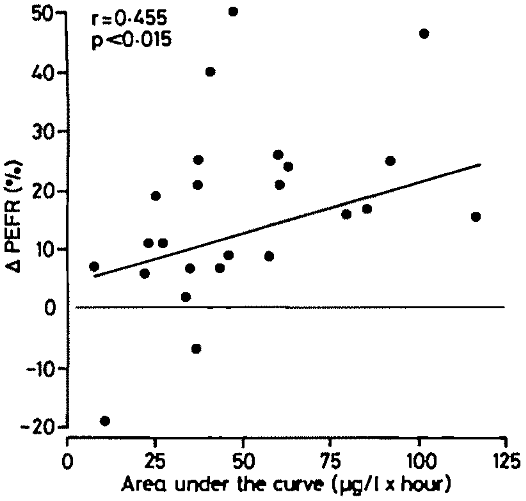

Fig 2 *Correlation between the difference in mean peak expiratory flow rate at treatment and baseline periods (Δ PEFR) and sodium cromoglycate area under the concentration time curve*

Table 3 *Correlations between pharmacokinetic and clinical parameters and technique of inhalation*

		r Value	*p Value*	*No of patients*
Area under the curve	*v* technique	0·798	<0 0005	24
Peak concentration of sodium cromoglycate	*v* technique	0·717	<0 0005	25
SCG 10 minute	*v* technique	0 652	<0 0005	25
Δ Score 0*	*v* technique	0 671	<0 0005	25
Δ DS†	*v* technique	0·410	<0·02	25
Δ PEFR‡	*v* technique	0 373	<0·035	25

*Δ Score 0=difference in percentage of symptomless days between baseline and treatment period, †Δ DS=difference in mean diary derived daily score for four symptoms between baseline and treatment period, ‡Δ PEFR=difference in mean peak expiratory flow rate between treatment and baseline period

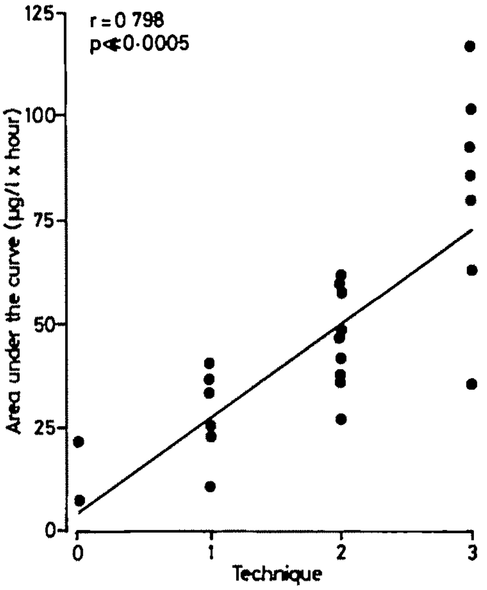

Fig 3 *Correlation between sodium cromoglycate area under the concentration time curve and technique of inhalation.*

Discussion

Measurement of sodium cromoglycate concentration enables one to determine the relation between drug concentration and response. As the site of action of this drug is not clinically accessible, measurement of sodium cromoglycate in the blood, apparently reflecting its concentration in the bronchioles, may be informative. Indeed, in normal volunteers it was shown that the concentrations in the blood rise rapidly after inhalation,[9] [10] whereas after oral ingestion blood concentrations are low,[9] thereby explaining the ineffectiveness of oral sodium cromoglycate in asthma.

Serum sodium cromoglycate concentrations in our young asthmatic patients rose after inhalation of 20 mg sodium cromoglycate and reached a mean peak of 51 μg/l, compared with a mean peak of 45 µg/l observed in adult volunteers.[9] Concentrations declined promptly to a mean of 13 µg/l at 120 minutes after inhalation, in a similar way to that observed in volunteers.[9–11] In contrast, Patel et al found that in asthmatic adults four successive inhalations of 5 mg sodium cromoglycate produced peak concentrations of only 5 µg/l which did not decline for 60 minutes after inhalation.[15] The reasons for this discrepancy are not clear.

A correlation was found between individuals' response and pharmacokinetic parameters. The Δ score D correlated significantly with all three pharmacokinetic parameters. The correlation between Δ PEFR and these three parameters was also significant, although of lower magnitude. The Δ DS correlated significantly only with the area under the curve which integrates concentration over time.

Spontaneous improvement during baseline period was observed as shown by the FEV_1 values, however, the correlation which was found between the response during the treatment period and the pharmacokinetic parameters argues for a direct relation between serum sodium cromoglycate concentration and the clinical response observed. Furthermore, this correlation provides evidence for the efficacy of sodium cromoglycate in this group of asthmatic children.

In an attempt to define the basis for the low sodium cromoglycate concentration in some patients, the technique of sodium cromoglycate inhalation was correlated with blood concentrations and with clinical response. Both pharmacokinetic parameters and clinical response correlated significantly with technique of inhalation. Brown *et al* have found that in normal volunteers the sodium cromoglycate area under the curve correlated with peak inspiratory flow rate, however, they state that variation in area under the curve and peak sodium cromoglycate is not solely explained by variation in peak inspiratory flow rate.[9] Similar data of intrasubject and intersubject variability were recently reported by Neale *et al.*[16] If technique of inhalation in someway or partly reflects peak inspiratory flow rate (which was not measured in our patients), one could argue that low sodium cromoglycate serum concentrations in some patients were the result rather than the cause of the poorer respiratory performance in the poorly responding patients. Peak inspiratory flow rate, however, falls only in severe obstructive airway disease, which did not occur in our patients. In addition, clinical response to sodium cromoglycate in our study was not related to the initial severity of disease. Two of seven patients with severe disease were poor responders (Δ score D <20%); this is similar to the proportion of poor responders in all the patients (seven out of 25, 28%).

It is not inconceivable, however, that severe airway obstruction may impede delivery of sodium cromoglycate to its target site of action. In such circumstances the use of a bronchodilator before inhalation of this drug or the use of special inhalation devices[17] may be considered and studied. No side effects of sodium cromoglycate were observed in this study, neither were dose related side effects observed in worldwide experience over many years.[3] Because response seems to be related to sodium cromoglycate concentrations in the blood, administration of larger doses than the recommended ones should also be considered.

This study shows that response to sodium cromoglycate is correlated to its concentration in the blood. Most of the non-responding patients have decreased concentrations of the drug, and in some of them this can be improved by additional training in proper use of the inhaler. There may yet be a few patients who do not respond even to apparently therapeutic concentrations of sodium cromoglycate.

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Severe hypoxaemia in pertussis

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SUMMARY Overnight tape recordings of breathing movements, airflow, and arterial oxygen saturation from six infants aged 3 weeks to 7 months, who had cyanotic episodes associated with pertussis, were compared with recordings from 12 age matched healthy controls. In all patients clinically apparent apnoeic episodes were associated with the rapid onset and progression of central cyanosis. When overnight recordings were compared, patients with pertussis had a greater frequency of apnoeic pauses (particularly those ≥12·0 seconds duration) and a greater frequency of episodes of hypoxaemia (oxygen saturation ≤80% for ≥0·5 seconds) associated with apnoeic pauses. In addition to episodes of hypoxaemia associated with a prolonged absence of breathing movements, patients with pertussis had frequent dips in oxygen saturation in association with continued breathing movements with and without continued inspiratory airflow. These episodes of hypoxaemia during continued breathing movements were more common in patients with pertussis

These findings suggest that episodes of abnormal apnoea accompanied by evidence of a mismatch between ventilation and perfusion of the lungs may produce the rapid onset of severe hypoxaemia in infants with pertussis.

Apnoeic and cyanotic episodes often occur during pertussis particularly when it occurs in early infancy.[1 2] The underlying mechanisms responsible for this dangerous complication are, however, unknown. In this paper we describe the results of an investigation by non-invasive techniques of infants with pertussis experiencing frequent and severe cyanotic episodes and compare these results with those from 12 healthy, age matched infants.

Patients and methods

Details of the six patients are given in the table. Pertussis was diagnosed by the presence of characteristic paroxysms of repetitive coughing that persisted for longer than one week and were associated with retching, vomiting, cyanosis, or convulsions in an infant who otherwise appeared to be in good health[3] Three patients had a history of recent exposure to pertussis Nasopharyngeal swabs ('Transwab', Medical Wire and Equipment Co) from all six patients were cultured on cephalexin supplemented charcoal agar and *Bordetella pertussis* was isolated from two patients. None of the patients had suffered episodes of cyanosis before the onset of the present illness.

All patients had a paroxysmal cough and a history of apnoea associated with the rapid onset of

Table *Clinical details of patients with pertussis*

Patient No	*Sex*	*Gestation (weeks)*	*Birth weight (g)*	*Age at onset of illness*	*Known exposure to pertussis*	*Results of culture for Bordetella pertussis*	*Presence of symptoms*			*Duration of illness at investigation (weeks)*
							Whoop	*Vomiting*	*Convulsions*	
1	F	40	2210	1 week	−	−	+	+	+	3
2	F	25	680	6 months	−	−	−	+	−	4
3	F	40	3030	3 months	−	+	−	−	−	2
4	M	40	3400	7 weeks	+	−	+	−	+	3
5	M	40	3780	3 weeks	+	+	−	+	+	1
6	F	37	2[illegible]00	4 months	+	−	+	+	+	2

profound cyanosis. These apnoeic cyanotic episodes began at least one week after the onset of cough in all patients except patient 1 who suffered apnoeic episodes from the outset of the illness In all patients the cyanotic episodes had a sudden unpredictable onset. They occurred when awake and when asleep and were often not immediately preceded by cough. In many cases coughing followed the onset of the cyanosis (see below). Patients 1, 4, 5, and 6 had a history of convulsions with loss of consciousness during their cyanotic episodes. Patients 1 and 6 were cyanosed and convulsing at the time of admission to hospital. (The twin sister of patient 6, with an identical history of pertussis, died during a cyanotic convulsion while the infants were being brought to hospital.) Apart from patient 2 who had a birthweight of 680 g at 25 weeks' gestation all the patients were delivered at term with birth weights of at least 2000 g.

All patients were nursed under close continuous supervision and were treated by positioning, oropharyngeal suctioning, and administration of oxygen via a face mask at the onset of any clinically apparent episodes of severe apnoea or cyanosis. Patients 1, 3, 5, 6 were treated with erythromycin, patients 1 and 3 were treated with phenobarbitone and salbutamol, and patients 4 and 5 were treated with aminophylline before and during investigation. Chest radiography showed normal results in all patients at the time of investigation. The recordings described in this paper were measured by non-invasive sensors, did not influence the clinical care of the patients, and were approved by the St George's Hospital ethical committee

The case history of patient 1 shows the clinical features seen in these six infants. This 3 week old girl was brought to hospital with a two week history of paroxysmal cough and repeated episodes of apnoea with cyanosis, loss of consciousness, and generalised convulsions. Cyanosis typically occurred within 10 seconds of the onset of apnoea and loss of consciousness and convulsions followed within a further 20 seconds. On the day of admission she had twice lost consciousness. On admission she was apnoeic, cyanotic, and convulsing but quickly recovered spontaneously. After admission she had further repeated episodes of apnoea, cyanosis, and convulsions requiring resuscitation by nursing and medical staff.

Healthy term infants being studied as part of a large survey of normal breathing patterns were used as control subjects. Two age matched controls were randomly selected for comparison with each patient with pertussis.

Investigations centered around overnight tape recordings (Racal Store 4 FM with a 1 channel multiplexer) of beat to beat arterial oxygen saturation (from a probe placed on the big toe and a modified Nellcor pulse oximeter Respox 2),[4] airflow measured at the external nares by a thermistor (time constant 0·3 seconds, Yellow Springs Instrument Co) or by expired carbon dioxide and a scavenger tube (sampling at 100 ml/minute, with an electronic response time of 100 milliseconds, Engstrom Eliza), and breathing movements from inductance plethysmography (Studley Data Systems) or a pressure capsule (Graseby Dynamics). In order to verify the accuracy of the oxygen saturation measurements the oximeter was used in a beat to beat mode and every plethysmographic waveform representing the arteriolar pulsation used to derive oxygen saturation was recorded onto the tape recordings along with the oxygen saturation signal Only oxygen saturation measurements accompanied by pulse waveforms of adequate quality were regarded as accurate.[4] In three infants (patients 1, 3, 5) oesophageal pressure was monitored by either a balloon catheter (PK Morgan with Furness controls pressure transducer) or a continuously infused (3 ml/hour) naso-oesophageal tube and pressure transducer (Gaeltec). In patient 1 an electroencephalogram was recorded from a centrotemporal configuration during cyanotic episodes. Tape recordings were printed onto an ink jet chart recorder (Siemens 34T) or an electrostatic chart recorder (Gould ES 1000).

Parents of patients and controls gave informed consent for the investigations

Recordings were analysed by a technician who was unaware of the clinical details of each subject. Periods during which signals were uninterpretable owing to movement artefact were documented and excluded from analysis. Breathing patterns were classified as regular or non-regular breathing according to previously published criteria.[5] Regular breathing was defined as episodes of ≥ 1 minute where the breathing pattern was relatively regular in amplitude and rate, interrupted by sighs but without movement artefact. Non-regular breathing was all the remainder of the recording, and included intermittent brief periods of movement artefact. All apnoeic pauses (absent inspiratory efforts for $\geq 4{\cdot}0$ seconds) were counted and their durations measured and the frequency of these pauses was determined by dividing the total number of pauses by the total duration of interpretable recording. All episodes of hypoxaemia, defined for this study as a situation where oxygen saturation fell to $\leq 80\%$ for $\geq 0{\cdot}5$ seconds were identified. This measurement was chosen after our experience of analysing similar recordings from large numbers of healthy infants wherein a cut off of 80% was helpful in defining normality. The duration of this hypoxaemia was measured for each episode and the breathing pattern during the preceding 12 seconds and during the period of hypoxaemia recorded. Breathing movements or airflow, or both, were regarded as absent if there was complete cessation for a period of ≥4·0 seconds. The frequency of episodes of hypoxaemia was determined by dividing the total number of episodes of hypoxaemia by the total duration of interpretable recording. The duration of hypoxaemia was determined by totalling the lengths of each episode and dividing this by the total duration of interpretable recording.

The frequency of apnoeic pauses of different durations, and the frequency of episodes of hypoxaemia associated with apnoeic pauses of different durations, in patients with pertussis and control subjects were compared by the Mann-Whitney U test.

Results

Clinical observations showed that although most of the overt cyanotic episodes began in association with coughing or crying, about one third, especially those occurring during sleep, began with an absence of inspiratory efforts (apnoeic pause). In all the observed cyanotic episodes the onset of cyanosis was rapid, usually occurring between four and eight seconds after the onset of the cough, crying, or apnoeic pause. Recovery from a cyanotic episode was frequently associated with a large inspiratory effort (a gasp).

All subjects had at least 4·9 hours of interpretable recordings (patients with pertussis 5·7–9·8 hours, normal subjects 4·9–12·5 hours.) Regular breathing and non-regular breathing alternated at intervals of about 20–100 minutes throughout the recordings. Both in the pertussis patients and in the normal subjects apnoeic pauses and episodes of hypoxaemia occurred almost exclusively during the periods of non-regular breathing.

Patients with pertussis had a greater mean frequency of apnoeic pauses than control subjects (fig 1). This difference was greatest for apnoeic pauses with a duration of ≥12·0 seconds ($p<0·005$). The longest apnoeic pauses for patients 1–6 were 15·0, 28·5, 11·5, 15·0, 53·8, and 17·0 seconds, respectively. The longest apnoeic pause in a control subject was 14·1 seconds. Thus five of the six patients had abnormally prolonged apnoeic pauses.

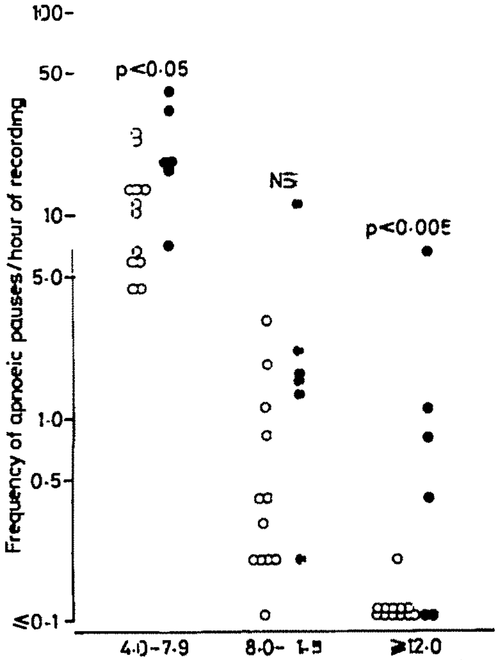

Fig 1 *Frequency of apnoeic pauses (duration 4·0–7·9, 8·0–11·9, ≥12·0 seconds) for patients with pertussis (solid circles), and control subjects (open circles). Note logarithmic scale on the vertical axis.*

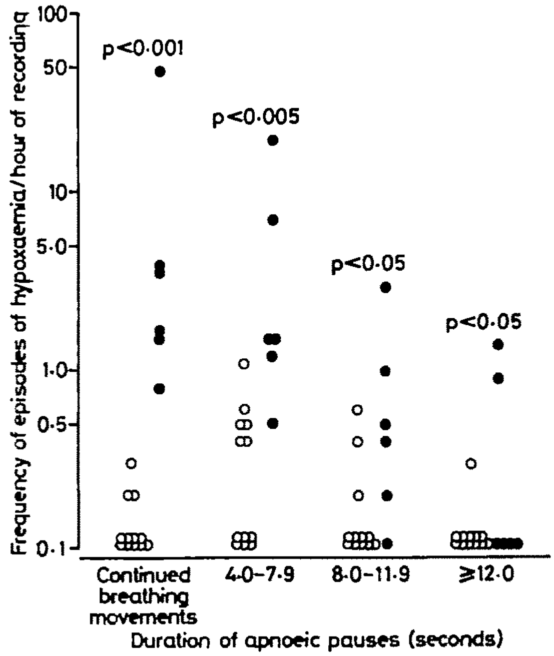

Fig 2 *Frequency of episodes of hypoxaemia associated with either continued breathing movements, or apnoeic pauses with durations of 4·0–7·9, 8·0–11·9, and ≥12·0 seconds, for patients with pertussis (solid circles), and control subjects (open circles). Note logarithmic scale on the vertical axis.*

The frequency of episodes of hypoxaemia related to the duration of associated apnoeic pauses for patients with pertussis and control subjects is shown in fig 2. Patients with pertussis had a greater frequency of episodes of hypoxaemia associated with apnoeic pauses with a duration of 4·0–7·9 seconds ($p<0.005$), 8·0—11·9 ($p<0.05$), and ≥12·0 seconds ($p<0.05$). The greatest difference between patients with pertussis and control subjects, however, was in the frequency of episodes of hypoxaemia during continued breathing movements ($p<0.001$).

An example of a hypoxaemic episode associated with a prolonged absence of breathing movements and airflow is shown in fig 3. These episodes usually began at end expiration and were associated with a raised oesophageal pressure. Prolonged apnoeic pauses often included a period of breathing movements without airflow before normal breathing was resumed ('mixed' apnoea) (fig 4). Some hypoxaemic episodes terminated with a period of sharply positive oesophageal pressure excursions suggesting coughing (fig 4). Patients with pertussis also had episodes of hypoxaemia associated with absent airflow despite continued breathing movements (fig 5). Patient 2 had prolonged periods of hypoxaemia despite continued breathing movements and continued airflow (fig 6) and patients 3–5 had similar but briefer episodes. Electroencephalographic recordings during prolonged pauses in inspiratory efforts with hypoxaemia in patient 1 did not show a seizure preceding the apnoeic pauses.

Discussion

All six patients in this study presented under 6 months of age and had cyanotic episodes characterised by the extremely rapid onset and progression

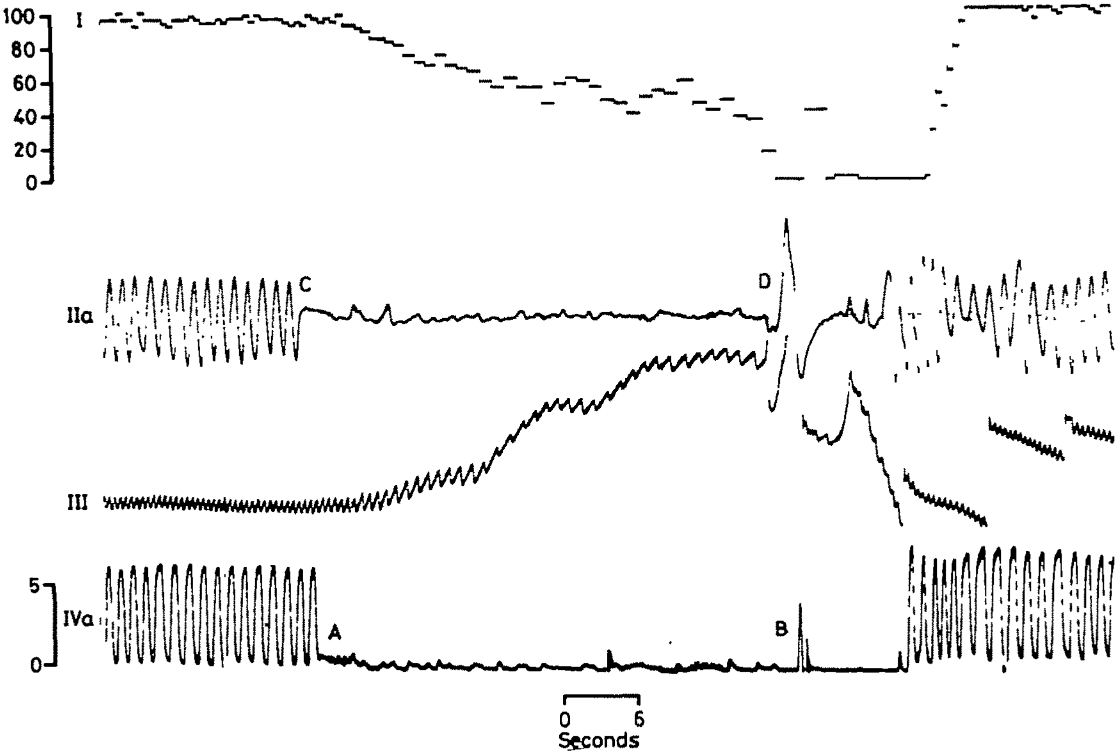

Fig 3 *Recording of an episode of severe hypoxaemia (saturated oxygen <50%) associated with a prolonged absence of airflow (A–B) and breathing movements (C–D) in patient 2 I Arterial saturated oxygen from a pulse oximeter scale is to the left of the signal (%). Total response time is about six seconds IIa Abdominal breathing movements from a pressure capsule transducer. expansion is an upward deflection III Arterial pulse waveform. adequate quality signals are present for most of the time during the fall in saturated oxygen A bradycardia is shown by increased intervals between the pulses IVa. Airflow at the nose represented by expired carbon dioxide signals. scale is to the left of the signal (vol %) Total response time is about two seconds*

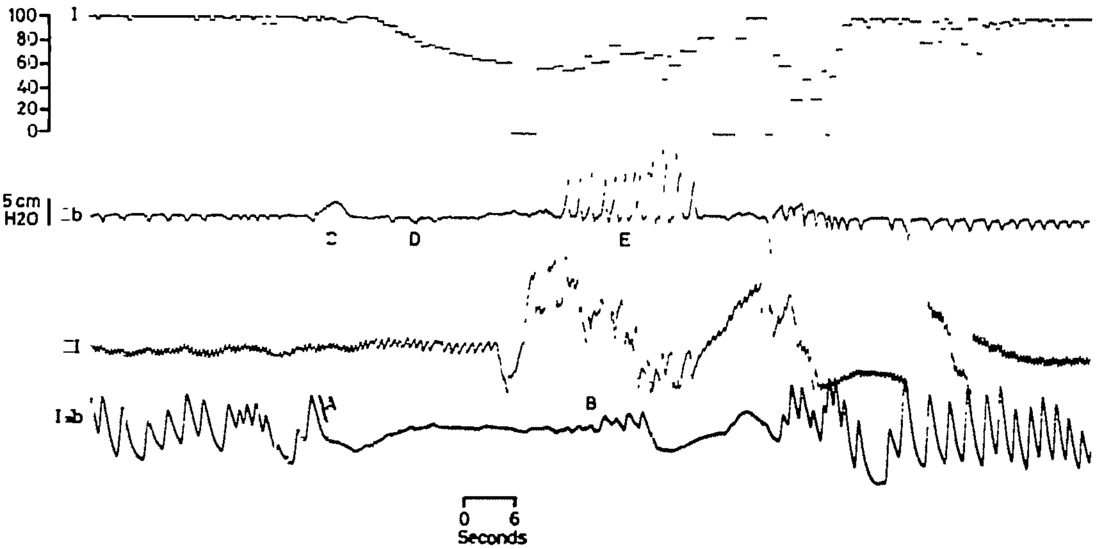

Fig 4 *Recording of an episode of hypoxaemia associated with 'mixed' apnoea in patient 5 A prolonged period of absent airflow (A–B) is initially associated with absent inspiratory efforts but a raised oesophageal pressure (C) Ineffective breathing efforts then occur (D). Towards the end of the episode there are sharply positive excursions in oesophageal pressure (E), suggestive of coughing I Arterial saturated oxygen. IIb Oesophageal pressure from a balloon catheter scale is to the left of the signal Positive pressure changes are represented by upward deflections III Arterial pulse waveform IVb Airflow at the nose from a thermistor inspiratory flows are represented by upward deflections*

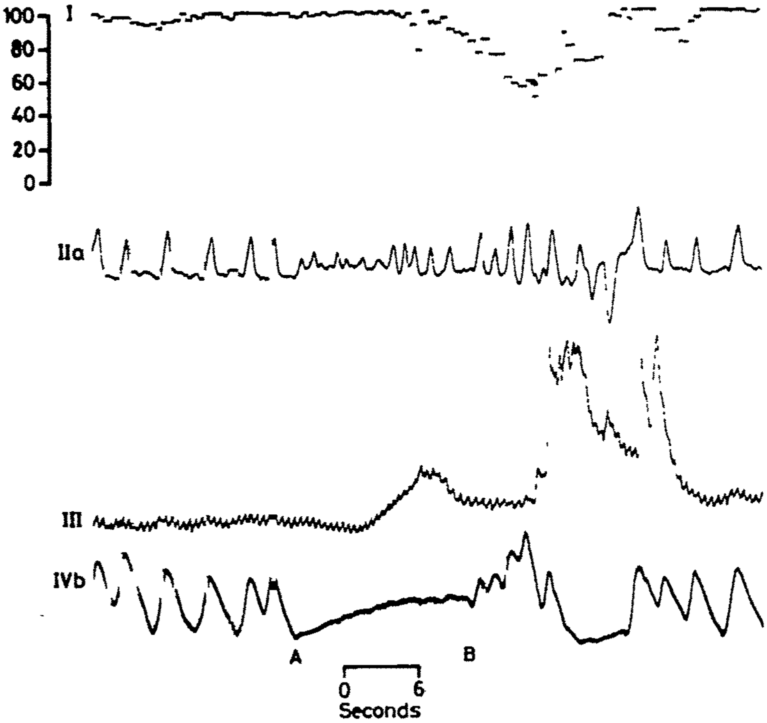

Fig 5 *Recording of an episode of hypoxaemia associated with continued breathing movements but absent airflow (A–B) in patient 4 I Arterial saturated oxygen IIa Abdominal breathing movements from a pressure capsule transducer expansion is an upward deflection III: Arterial pulse waveform IVb: Airflow at the nose from a thermistor inspiratory flows are represented by upward deflections.*

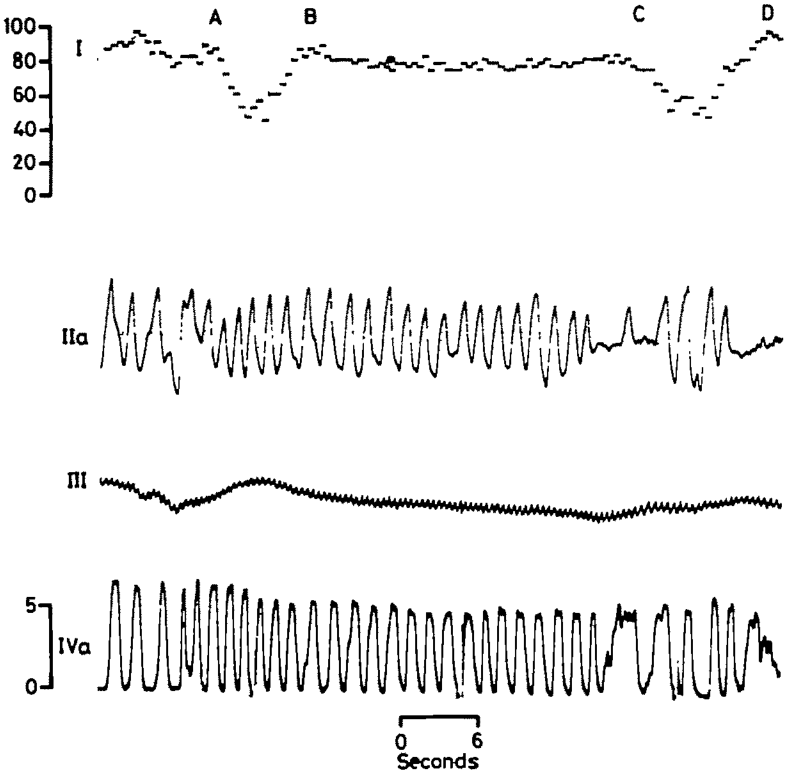

Fig 6 *Recording of two episodes of hypoxaemia (A–B) and (C–D) associated with continued breathing movements and continued airflow in patient 2 I. Arterial saturated oxygen IIa Abdominal breathing movements from a pressure capsule expansion is an upward deflection III Arterial pulse waveform. IVa Airflows at the nose represented by expired carbon dioxide signals.*

of severe hypoxaemia similar to that occurring during a condition previously termed prolonged expiratory apnoea[6–9] and suggesting the acute onset of a mismatch between ventilation and perfusion of the lungs. Between clinically overt cyanotic events infants with pertussis showed repeated abnormal dips in arterial oxygen saturation in association with four breathing patterns: prolonged (≥15 seconds) pauses in inspiratory efforts (fig 3), an initial absence of effort and airflow followed by continued efforts but absent airflow (fig 4), continued breathing efforts but absent inspiratory airflow (fig 5), and continued inspiratory efforts and continued airflow (fig 6). Hypoxaemia was not seen in association with these patterns of breathing in control subjects As with the rapidity of onset and severity of the clinically apparent cyanotic episodes, the occurrence of hypoxaemia during continued breathing movements is also characteristic of prolonged expiratory apnoea,[6 7] and suggests that both mismatch between ventilation and perfusion of the lungs, and apnoea (absent ventilation of the lungs) contribute to the pathogenesis of hypoxaemia in infants with pertussis.

We have previously suggested that alveolar atelectasis may be responsible for these disturbances in ventilatory perfusion relations and that the accompanying prolonged pauses in breathing movements may result from the effects of atelectasis on lung reflexes.[7 8] This hypothesis is supported by the recordings shown in fig 6, which shows that hypoxaemia may develop despite continued airflow into the lungs. If alveolar atelectasis is the cause of the hypoxaemic episodes, a defect in lung surfactant may represent the primary pathology.[7–9] In infants with pertussis this may be due to a direct effect of *B pertussis* toxins on surfactant synthesis, secretion or function.

Although a proportion of the cyanotic events began during coughing, some followed crying, and others, especially during sleep, followed a pause in inspiratory efforts. In this last case the infant would characteristically stop breathing, become cyanosed, arouse, and then begin coughing.

Cyanotic convulsions have been reported to precede death in pertussis,[10] and changes suggesting anoxia are a consistent finding in the histology of the brains of children dying of pertussis complicated by convulsions.[11] Our recordings suggest that the convulsions are secondary to severe cerebral hypoxaemia.

The patterns of breathing and hypoxaemia identified above have been described in apnoea of prematurity suggesting that the pathogenesis of these two conditions might be similar.[12] Moreover, similar cyanotic episodes, sometimes with evidence of prolonged pauses in inspiratory efforts, have been reported in other respiratory tract infections during infancy. In two retrospective studies respiratory syncytial virus infection was associated with prolonged apnoea or cyanotic episodes in 10% and 20% of cases respectively.[13 14] In the prospective study of infection by respiratory syncytial virus reported by Anas *et al*, 25% of infants showed prolonged apnoeic episodes.[15] These often began early in the disease before other symptoms of infection had developed and were more frequent in infants less than 3 months of age and in previously preterm infants especially those who had suffered from apnoea of prematurity. Yolken and Murphy described cyanotic episodes in five infants with rotavirus infection, three of whom were temporarily resuscitated but subsequently died.[16]

Despite a distinctive clinical picture, doctors are often slow to diagnose pertussis,[17] and notifications greatly underestimate the true incidence of the disease.[18] Even when pertussis is diagnosed, however, clinical observation alone is likely to greatly underestimate the frequency and severity of hypoxaemia as shown by our overnight recordings.

Nicoll and Gardner[19] and Cherry[20] have suggested, on the basis of epidemiologic studies, that pertussis may be responsible for some cases of sudden infant death. Williams and Jones have produced evidence that the convulsions and apnoea complicating pertussis may be accompanied by subsequent intellectual impairment.[21] These data and our findings suggest that infants with a history of cough with apnoea or cyanosis, even if apparently well at initial examination, should be admitted to hospital for a period of meticulous observation. Our results also underline the need to prevent this serious and as yet untreatable infectious disease and clearly this can be best achieved by a more complete programme of immunisation.

In conclusion episodes of abnormal apnoea accompanied by evidence of a mismatch between ventilation and perfusion of the lungs may cause severe arterial hypoxaemia in infants with pertussis. This hypoxaemia may be life threatening, may result in seizures, and may be one cause of the brain damage reported in some infants with pertussis.

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Age dependence of flow velocities in basal cerebral arteries

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SUMMARY Flow velocities in the basal cerebral arteries were studied by transcranial Doppler sonography. A longitudinal study was undertaken on 25 healthy newborn babies during the first 20 days of life, and a cross sectional study was performed on 112 healthy children between 1 day and 18 years of age. A rapid linear increase of flow velocities was found within the first 20 days with higher velocities in neonates of higher birth weight and gestational age. Maximal values were recorded at the age of 5 to 6 years. After that the velocities decreased linearly to 70% of their maximum at the age of 18 years. Reference values were derived from the data considering age and birth weight. The increasing flow velocities probably reflect the increasing cerebral blood flow during the first years of life. Our results also support the hypothesis of a decrease in cerebrovascular resistance during infancy. With the technique of transcranial Doppler sonography and the introduced reference values normal and abnormal intracranial flow velocities can now be assessed by non-invasive methods in all paediatric age groups.

Since the report by Bada *et al*[1] many Doppler sonographic studies have been undertaken to evaluate cerebral blood flow in neonates at risk for perinatal brain injury.[2] Because of technical difficulties the recording of flow velocities in the intracranial arteries by Doppler sonography has been restricted to neonates and young infants. The new technique of transcranial Doppler sonography combines a low emitting frequency with the pulsed Doppler technique,[3] and by this method flow velocities in the basal cerebral arteries now can be determined at any age. So far this has been done systematically only in adults.[4]

In childhood the thinner bones facilitate the penetration of ultrasound through the skull. For that reason the registration of signals by transcranial Doppler sonography is easier than in adults. The examination technique, however, must be adapted to the size of the child's head. The changing intracranial haemodynamics during infancy and childhood require age dependent reference values in order to distinguish physiological and pathological flow velocities in the basal cerebral arteries.

Subjects and methods

Twenty five healthy preterm and term neonates with a mean (SD) birth weight of 2248 (776) g (range 1170–4150 g) and a postconceptional age of 35·6 (3·0) weeks (range 28–41 weeks) were examined by transcranial Doppler sonography in a longitudinal study on days 1, 2, 3, 4, 7, 10, 15, 20, 25 of age. Systolic, mean, and diastolic arterial blood pressure and heart rate were measured simultaneously (Dinamap 847). In a cross sectional study, 112 healthy children between 1 day and 18 years of age were examined by transcranial Doppler sonography. Cerebral sonography (ATL Mark 100) was performed in all children under 1 year and showed no disease.

Doppler recordings were made with an EME TC 2–64 system with a pulsed 2 MHz Doppler probe and an integrated Fast Fourier real time frequency analyser (sliding average technique, 64 frequency points, 132 spectral lines). The system requires no calibration because of digitalised signal processing. Frequency to blood flow velocity conversions are assuming an insonation angle of zero.

The examination technique for children over 1 year old was the same as for adults.[3] [4] Middle cerebral artery, internal carotid artery, anterior cerebral artery, posterior cerebral artery with its precommunicating (P1) and postcommunicating (P2) part and basilar artery were recorded.

In children under 1 year old middle cerebral, anterior cerebral, and internal carotid artery were recorded. The position of the Doppler probe for registration of the middle cerebral artery was the same as in older children. The internal carotid artery was recorded with the Doppler probe on the anterior fontanelle directing the ultrasonic beam to the angle of the lower jaw. The extracranial part of the internal carotid artery (flow towards the probe) was identified beside the jugular vein (flow away from the probe). In following the extracranial part of the internal carotid artery by reducing the depth of the sample volume the intracranial part of the internal carotid artery was found. The postcommunicating part of the anterior cerebral artery was recorded with a probe position high frontally in the midline directing the ultrasonic beam caudally and slightly backwards. Probe position, depth of the sample volume, direction of flow and, in some older children, compression tests were used for vessel identification.[3 4]

Systolic peak flow velocity, mean flow velocity (time-mean of the maximum velocity envelope curve[3]) and end diastolic peak flow velocity were recorded. The pulsatility index (PI) was calculated according to the formula PI=(S–D)/S, where S and D are systolic and end diastolic peak flow velocity.

Children under 1 year old were asleep, those over 1 year were awake during Doppler sonography. All children were studied in a horizontal position with the head in the midline. Only constant recordings of at least 15 seconds duration were analysed

Mean reference values were calculated for flow velocities in middle cerebral, internal carotid, and anterior cerebral artery. Mean reference values for the first 20 days of life for different birth weights were derived from the data of the longitudinal study Linear relations between flow velocities on day 1 and birth weight were found. The derived equations were used to calculate weight dependent values of each flow velocity for the first day of life. From the linear relations between flow velocities and age the mean daily increase of each flow velocity was calculated and added to the weight dependent velocities of the first day of life. Mean reference values of flow velocities from 0–18 years were derived from the cross sectional study by an equation of non-linear parameters.[5]

The study was approved by the hospital ethical committee

Results

In total 337 Doppler studies were carried out. Altogether 1347 vessels were insonated resulting in recordings of 4041 flow velocities. Depending on age and head size the basal cerebral arteries were found at different distances from the Doppler probe (table 1). Bilateral examination of corresponding arteries showed variation of flow velocities between 2% and 8% intraindividually.

During the first 20 days of life all flow velocities increased linearly. The average daily increase of systolic peak flow velocity, mean flow velocity, and end diastolic peak flow velocity was about 1·5, 0·8, and 0·4 cm/second, respectively with no significant difference for various birth weights (table 2). On average the pulsatility indices increased slightly from 0·69 to 0·72 within this time. The mean values of systolic, mean, and end diastolic arterial blood pressure of all children increased significantly from 54/43/32 mm Hg on day 1 to 75/57/44 mm Hg on day 20.

Beyond the 3rd week of life flow velocities increased less quickly. Maximal velocities, which were about three to four times as high as those of the first days of life, were found at an age of 5–6 years. After that flow velocities decreased to about 70% of the maximal velocities by the age of 18 years. On average the pulsatility indices decreased from 0·70

Table 1 *Age dependent distances between Doppler probe and cerebral arteries (mm)*

Age	*Middle cerebral artery*	*Internal carotid artery*	*Anterior cerebral artery*	*Posterior cerebral artery*		*Basilar artery*
				*P1**	*P2†*	
0–3 months	25	55–65‡	25–30§	—	—	—
>3–12 months	30	60–70‡	30§	—	—	—
>1–3 years	30–45	40–50	55–65	55	50–55	50–60‖
>3–6 years	40–45	45–55	60–65	55–60	50–60	55–70‖
>6–10 years	45–50	50–55	60–70	60–70	55–65	55–75‖
>10–18 years	45–50	55	65–75	60–70	60–65	60–80‖

*Precommunicating part of the posterior cerebral artery
†Postcommunicating part of the posterior cerebral artery
‡Insonation of the vessel through the anterior fontanelle
§Insonation of the vessel from high frontally.
‖Insonation through the occipital foramen
The other vessels were insonated through the temporal bone

Table 2 *Mean (SD) flow velocities in basal cerebral arteries (in cm/second) of a longitudinal study of normal preterm and term neonates (n=25)*

	Day 1	*Day 5*	*Day 10*	*Day 15*	*Day 20*
Middle cerebral artery:					
Systolic peak flow velocity	42 (10)	54 (10)	61 (13)	64 (10)	70 (13)
Mean flow velocity*	22 (6)	26 ([illegible])	30 (6)	32 (6)	37 (7)
End diastolic peak flow velocity	13 (4)	15 (3)	16 (3)	17 (5)	19 (6)
Internal carotid artery:					
Systolic peak flow velocity	35 (6)	44 (10)	51 (8)	52 (8)	62 (8)
Mean flow velocity*	18 (5)	22 (5)	27 (5)	28 (4)	33 (5)
End diastolic peak flow velocity	11 (4)	12 (3)	14 (3)	14 (3)	16 (3)
Anterior cerebral artery:					
Systolic peak flow velocity	32 (7)	42 (7)	44 (8)	52 (7)	57 (7)
Mean flow velocity*	17 (5)	21 (6)	23 (5)	27 (5)	31 (3)
End diastolic peak flow velocity	11 (5)	13 ([illegible])	13 (3)	16 (5)	16 (2)

*Mean flow velocity=time-mean of the maximal velocity envelope curve

Table 3 *Mean (SD) flow velocities in basal cerebral arteries (in cm/second) in a cross sectional study of healthy children (n=112)*

Age	*n*	*Middle cerebral artery*	*Internal carotid artery*	*Anterior cerebral artery*	*Posterior cerebral artery*		*Basilar artery*
					*P1**	*P2†*	
Systolic peak flow velocity:							
0–10 days	18	46 (10)	47 (9)	35 (8)	—	—	—
11–90 days	14	75 (15)	77 (19)	58 (15)	—	—	—
3–11·9 months	13	114 (20)	104 (12)	77 (15)	—	—	—
1–2·9 years	9	124 (10)	118 (24)	81 (19)	67 (18)	69 (9)	71 (6)
3–5·9 years	18	147 (17)	144 (19)	104 (22)	84 (20)	81 (16)	88 (9)
6–9·9 years	20	143 (13)	140 (14)	100 (20)	82 (11)	75 (10)	85 (17)
10–18 years	20	129 (17)	125 (18)	92 (19)	75 (16)	66 (10)	68 (11)
Mean flow velocity‡:							
0–10 days	18	24 (7)	25 (6)	19 (6)	—	—	—
11–90 days	14	42 (10)	43 (12)	33 (11)	—	—	—
3–11·9 months	13	74 (14)	67 (10)	50 (11)	—	—	—
1–2·9 years	9	85 (10)	81 (8)	55 (13)	50 (17)	50 (12)	51 (6)
3–5·9 years	18	94 (10)	93 (9)	71 (15)	56 (13)	48 (11)	58 (6)
6–9·9 years	20	97 (9)	93 (9)	65 (13)	57 (9)	51 (9)	58 (9)
10–18 years	20	81 (11)	79 (12)	56 (14)	50 (10)	45 (9)	46 (8)
End diastolic peak flow velocity:							
0–10 days	18	12 (7)	12 (6)	10 (6)	—	—	—
11–90 days	14	24 (8)	24 (8)	19 (9)	—	—	—
3–11·9 months	13	46 (9)	40 (8)	33 (7)	—	—	—
1–2·9 years	9	65 (11)	58 (5)	40 (11)	36 (13)	35 (7)	35 (6)
3–5·9 years	18	65 (9)	66 (8)	48 (9)	40 (12)	35 (9)	41 (5)
6–9·9 years	20	72 (9)	68 (10)	51 (10)	42 (7)	38 (7)	44 (8)
10–18 years	20	50 (8)	59 (9)	46 (11)	39 (8)	33 (7)	36 (7)

*Precommunicating part of posterior cerebral artery.
†Postcommunicating part of posterior cerebral artery.
‡Mean flow velocity=time-mean of the maximal velocity envelope curve.

to 0·55 during the first year of life and remained nearly unchanged beyond infancy. At all ages the flow velocities decreased in the sequence: middle cerebral artery, internal carotid artery, anterior cerebral artery, basilar artery, posterior cerebral artery (table 3). Mean reference values of flow velocities in the middle cerebral, internal carotid, and anterior cerebral artery were derived from the data as described above (figs 1 and 2). Velocities not differing more than 30% from these

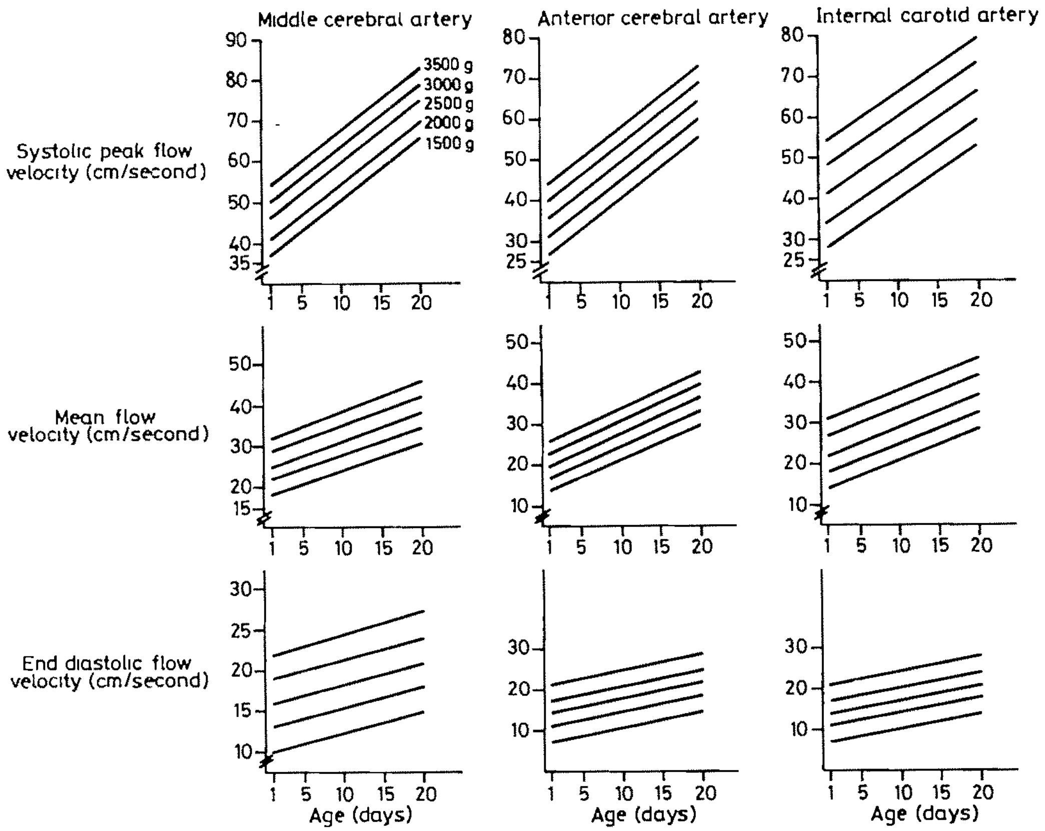

Fig 1 *Mean reference values of flow velocities in basal cerebral arteries from 1–20 days of age for different birth weights*

values were considered as being within the reference range.

Discussion

For the first time we present flow velocities and pulsatility indices in the basal cerebral arteries recorded by transcranial Doppler sonography in healthy children of 0–18 years of age. Our results are comparable with recordings obtained by other Doppler techniques.[6 7] Spectral mean flow velocities of 10·5 cm/second in the anterior cerebral artery and of 10 cm/second in the internal carotid artery were found in a population with comparable gestational age and a mean postnatal age of 5 days.[6] In the same study the end diastolic peak flow velocities in the anterior cerebral and internal carotid artery were 10·8 and 9·5 cm/second respectively.[6] In children 10–18 years old we recorded flow velocities, which were 15–30% higher than those of adults.[3 4]

Owing to the strong dependence on age and birth weight, Doppler sonography of many more children would be required to determine 'exact' normal values. The mean reference values presented here, however, indicate the flow velocities to be expected for different ages and birth weights The derived reference ranges prove useful in detecting abnormal flow conditions.

Newborn babies with higher birth weights might be expected to have a less rapid increase of flow velocities after birth. Our data do not support this assumption. For calculating reference values we therefore supposed a weight independent increase of flow velocities during the first 3 weeks of life The justification for this approach is given by the good correspondence between the recorded data and the calculated reference values (tables 2 and 3 and figs 1 and 2).

Principles and techniques of transcranial Doppler sonography have been discussed elsewhere.[3 4] The absolute value of the Doppler shift depends on the cosine of the angle between ultrasonic beam and insonated vessel. In transcranial Doppler sonography angles of insonation well below 30 degrees are

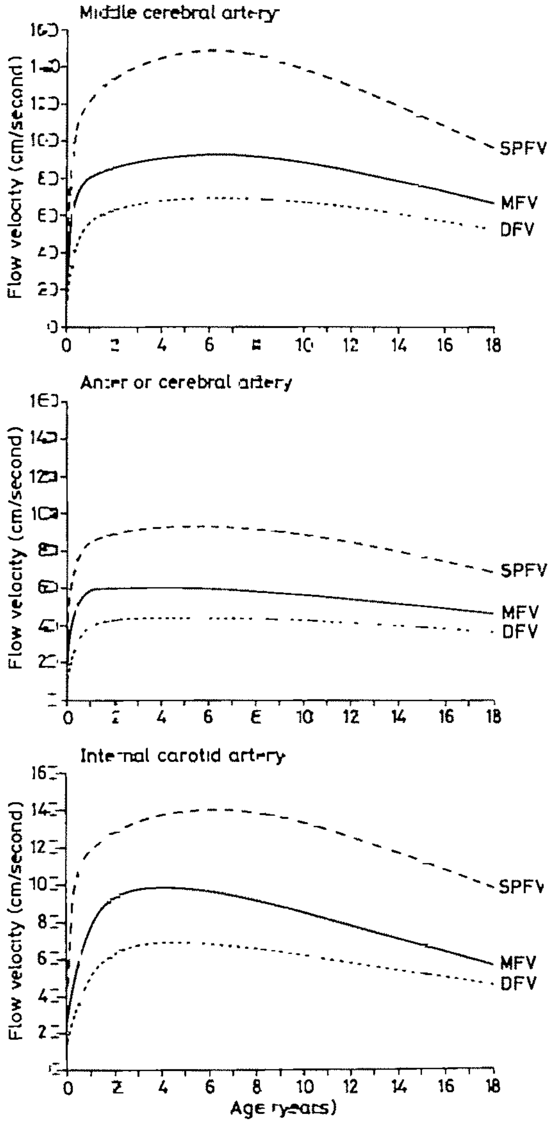

Fig 2 *Mean reference values of flow velocities in (a) middle cerebral artery, (b) internal carotid artery, and (c) anterior cerebral artery from 0 to 18 years of age. SPFV=systolic peak flow velocity; MFV=mean flow velocity (time-mean of the maximal velocity envelope curve), and DFV=end diastolic peak flow velocity*

used The cosine of 30 degrees is 0·87. That is why the recorded flow velocities deviate less than 13% from the true velocities.

The flow volume through a vessel is the product of the spectral mean flow velocity and the cross sectional area of the vessel. The former is about half of the time mean of the maximum velocity envelope curve.[3] As the individual cross sectional area of the basal cerebral arteries cannot be determined exactly the individual flow volume through the basal cerebral arteries cannot be calculated quantitatively by any Doppler sonographic method. Cerebral blood flow (in ml/100 g brain weight/minute), however, is proportional to the quotient: blood flow velocity x cross sectional area of basal cerebral arteries divided by brain weight.

We will not discuss in detail the adaption of human cerebral haemodynamics to birth and early extrauterine life. Vasoactivity of the major intracranial arteries and of the cerebral arterioles are supposed to have an important influence on flow velocities and pulsatility indices during this time.[9–11]

The cross sectional area of the basal cerebral arteries in young adults is three times higher than that of newborn babies.[12 13] The adult values are reached at the age of 6 years The brain weight trebles during the first 6 years of life [14] From this relatively constant ratio of the cross sectional area of the basal cerebral arteries and brain weight one can derive a proportionality between cerebral blood flow and blood flow velocities during the first 6 years of life. The recorded velocities increase three to four fold during this time, which is comparable with the wide range of values for cerebral blood flow [6 15 16] Similarly we see the higher flow velocities of term neonates compared with premature babies as a sign of a higher cerebral blood flow

The capillary density in the brain doubles during the first year of life,[17] and the histological structure of the basal cerebral arteries changes.[18] These alterations cause a decrease in cerebrovascular resistance during infancy. The pulsatility index to some extent indicates the vascular resistance.[19 20] The decrease in pulsatility index of the basal cerebral arteries during infancy may reflect the decrease of cerebrovascular resistance.

So far Doppler sonography of intracranial arteries has been used mostly in neonates With the aid of transcranial Doppler sonography it can be extended to older children with problems such as bacterial meningitis (severe forms with extremely increased flow velocities due to vessel narrowing); acute hemiplegia; migraine (reduced or increased flow velocities on the affected side depending on the underlying pathology and stage of the disease), increased intracranial pressure (decreased flow velocities); cerebral death (reverberating flow pattern), etc. Our data and reference values help to distinguish normal and abnormal intracranial flow conditions in all paediatric age groups. The already developed continuous recording facilities will allow closer monitoring of cerebral haemodynamics in children receiving intensive care.

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Serological evaluation of a measles, mumps, and rubella vaccine

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SUMMARY Combined measles, mumps, and rubella vaccination is soon to become available in Britain in the routine immunisation programme. A controlled study was performed in 319 children, aged 13 months, to assess the antibody response and clinical reactions to a new combined measles, mumps, and rubella vaccine in comparison with a single component measles vaccine. In the children who received the combined vaccine, seroconversion was established in 93% for measles, 99% for rubella, and 100% for mumps. In the children who received the single measles vaccine, seroconversion was established in 92% for measles and in none for rubella and mumps. There was no increase in clinical reactions after the measles, mumps, and rubella vaccine compared with the measles vaccine.

These results suggest that this combined vaccine would be effective and safe in a British population and give further support for the introduction of the combined measles, mumps, and rubella vaccine to Britain.

The inadequate immunisation policies in Britain, particularly immunisations against measles and rubella, have had considerable coverage in recent literature.[1-7] By 1984, the national measles immunisation rate had reached only 63%[8] and there is still significant morbidity from the disease. Selective immunisation of schoolgirls and non-immune adult women against rubella has reduced the incidence of congenital rubella syndrome, but there is evidence that immunisation of all young children is needed to reduce this further.[9 10]

It has been suggested that a new strategy for immunisation against measles, mumps, and rubella should be introduced into Britain with the aim of eradicating all three diseases.[1 2] A combined measles, mumps, and rubella vaccine has been used routinely in the United States since the 1970s and in Sweden and Finland since 1982. It has been shown to be safe and effective. British public opinion is still very sensitive to reports of adverse reactions to the pertussis vaccine and it is difficult to predict the response to another 'new' vaccine. It has been postulated that parents might find a combined vaccine a more attractive option than the single measles vaccine.[1 2 9]

The Department of Health has recently (April 1987) agreed to the introduction of the combined measles, mumps, and rubella vaccine in principle. It is therefore important to establish the efficacy and safety of the combined vaccine in Britain. Before the vaccine is used routinely in this country it is also vital that its potential uptake is assessed because an uptake of 85% is needed to achieve herd immunity.[9] We report the results of a controlled trial of a new combined vaccine in comparison with a single measles vaccine in a British population. We assessed the rate of seroconversion and the occurrence of clinical reactions in 319 children aged 13 months. We were also interested in the general response to the trial and the combined vaccine.

Subjects and methods

Before the trial started all health visitors, general practitioners, and clinical medical officers were informed of the trial and the purpose of the combined vaccine. Names of children due to receive the measles vaccine within the following 2–3 months were obtained from the Oxfordshire Health Authority immunisation computer programme. The parents of all children attending various large clinics throughout Oxfordshire were approached by letter. The letter gave a brief explanation of the study and parents were asked to complete a short questionnaire. If the parents expressed an interest in the study they were visited at home by the investigators and the study was explained in more detail. If they agreed for their child to participate they completed a written assent.

The parents were offered the choice of which vaccine their child would receive (the combined measles, mumps, and rubella vaccine or the single measles vaccine). Random allocation was planned if the parents had no preference. Children with a definite history of measles, mumps, or rubella were excluded from the trial, as were any children who had a history of convulsions, immunosuppression, or severe allergy to egg, neomycin or kanamycin. The immunisation was postponed if the child had an acute febrile illness.

The children were immunised at the age of 13 months. The combined vaccine used contained the Schwarz (measles), Urabe AM/9 (mumps), and the Wistar RA 27/3 (rubella) live attenuated virus strains. The single measles vaccine contained the Schwarz strain The vaccines were reconstituted immediately before use with 0·5 ml of diluent and administered into the anterolateral aspect of the upper thigh. Both vaccines were produced by Institut Merieux. A venous blood sample (1·5 ml) was taken immediately before the immunisation and then again about six weeks later. Parents were informed of the nature and timing of possible reactions and were asked to complete a diary, recording any symptoms or signs in the child (regardless of whether they thought it was caused by the vaccine) The parents assessed the child's temperature by touch and recorded a fever if the child felt hotter than usual.

All serological assays were performed in the laboratories of Institut Merieux in Lyon, France Before testing the samples were stored at −20°C and transported to the laboratories on dry ice The assays were performed under code so that the laboratory did not know which vaccine had been given

The measles and rubella antibody titres were determined by haemagglutinin inhibition techniques. The initial dilution was 1 in 10. The mumps antibody titres were determined by the enzyme linked immunosorbent assay (ELISA) using the Behring kit. The initial dilution was 1 in 80. The serological results for each child were sent to the child's parents and reimmunisation was offered to those who had not seroconverted.

Statistical analysis of the incidence of clinical reactions in the two vaccine groups was compared by χ^2 with Yates's correction.

The trial was approved by the local ethics committee.

Results

Letters were sent to 904 parents of whom 642 (71%) returned the questionnaires. Of the 642 replies, 362 (40% of the total letters sent) expressed an interest in participating in the trial, 260 (29%) did not want to participate, and 20 (2%) had moved from the area.

Of the 362 children whose parents were initially interested in the trial, 27 were excluded for various medical reasons and 20 parents changed their mind about participating This left 315 children who were recruited into the trial. A further four children who had been directly referred by health visitors were also recruited. This gave a total of 319 children: 263 (82%) received the measles, mumps, and rubella vaccine and 56 (18%) the single measles vaccine. This meant that 259 (29%) of the original parents approached agreed for their child to be given the combined vaccine in a trial that involved two venepunctures. No parent was undecided as to which vaccine their child should have. The mean age of the children at time of immunisation was 13·1 months. The male to female ratio was 1·2:1.

SEROLOGICAL RESULTS

Preimmunisation blood samples were obtained from 236 (90%) of the children given the measles, mumps, and rubella vaccine and from 52 (93%) of those given the measles vaccine The numbers of children with preimmunisation antibodies against measles, mumps, and rubella for both vaccine groups are shown in table 1.

Postimmunisation blood samples were obtained from 218 (83%) of the combined vaccine group and 48 (86%) of the measles vaccine group. The average time between the immunisation and the second blood sample was 42 days. Some of the postimmunisation samples were insufficient for all three antibody assays. In the measles vaccine group there was one sample from which just a measles titre was obtained. In the combined vaccine group there was one sample from which only a measles titre was obtained and four samples from which only measles and rubella titres were obtained. The seroconversion rates in initially seronegative children are shown in table 2

Table 1 *Children with preimmunisation antibodies*

Vaccine group	*No(%) with antibody present*		
	Measles	*Rubella*	*Mumps*
Measles (n=52)	1 (2)	1 (2)	5 (10)
Measles, mumps, rubella (n=236)	2 (1)	5 (2)	28 (12)

Seroconversion was taken as a change from a titre of <10 preimmunisation to a titre of ≥20 postimmunisation for the measles and rubella assays and a change from <80 to ≥160 in the ELISA mumps assay.

The frequency distribution of the postimmunisation titres and the geometric mean titres for the measles, mumps, and rubella vaccine and the measles vaccine are shown in the figure.

CLINICAL FINDINGS

The incidence of signs and symptoms recorded during the three week period postimmunisation are shown in table 3. Only about 10% of the children has no symptoms during this time. The most commonly reported symptoms were irritability, rash, coryza and fever, followed by lethargy, diarrhoea, anorexia, and cough

The symptoms of irritability, fever, and rash were most noticeable between the ninth and 13th days after immunisation, however, a suggestion of

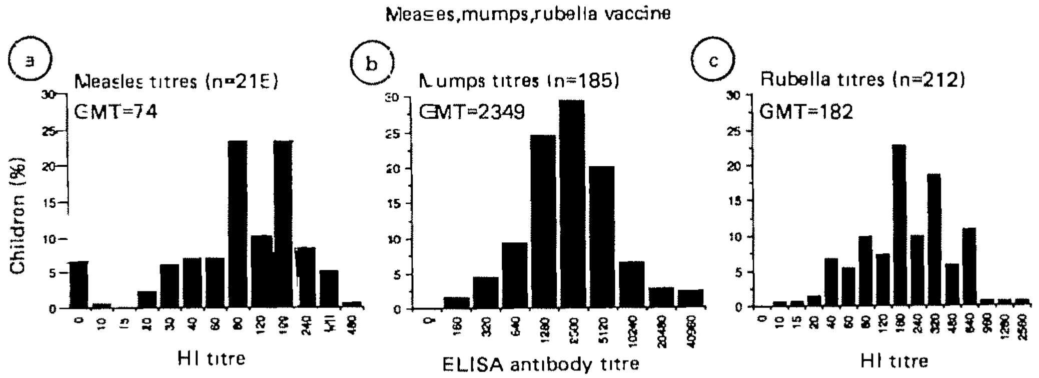
Table 2 *Seroconversion rates in initially seronegative children*

Vaccine group	*No(%) who seroconverted*		
	Measles	*Rubella*	*Mumps*
Measles	44/48 (92)	0/46	0/42
Measles, mumps, and rubella	200/215 (93)	211/212 (99)	185/185 (100)

Table 3 *No (%) of children with symptoms and signs in the three weeks after immunisation*

Symptoms and signs	*Measles, mumps, rubella vaccine (n=263)*	*Measles vaccine (n=56)*
Irritability	175 (67)	40 (71)
Rash	109 (41)	23 (41)
Coryza	104 (40)	27 (48)
Fever	88 (34)	16 (29)
Cough	40 (15)	12 (21)
Lethargy	65 (25)	13 (23)
Diarrhoea	55 (21)	10 (18)
Vomiting	33 (13)	7 (13)
Anorexia	48 (18)	14 (25)
Conjunctivitis	23 (9)	5 (9)
Lymphadenopathy	6 (2)	0
Parotitis	3 (1)	0
Local reaction	14 (5)	4 (7)
No symptoms	33 (13)	4 (7)
Child given paracetamol	156 (59)	29 (52)
seen by a doctor	42 (16)	11 (20)

No significant differences were found



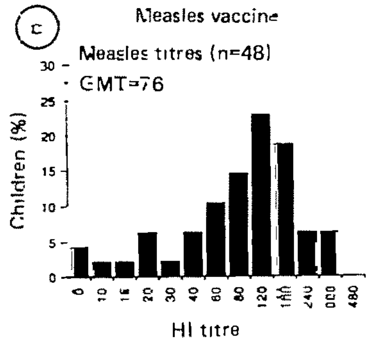


Figure *Frequency distribution of postimmunisation antibody titres and geometric mean titres (GMT), for the measles, mumps, and rubella vaccine and the measles vaccine HI=haemagglutinin inhibition* clustering between the second and fifth days also occurred. This triad of symptoms, often with associated coryza and sometimes cough, occurred in 38 (14%) of the combined vaccine group and in nine (16%) of the measles group. The symptoms of anorexia, lethargy, diarrhoea, and vomiting did not show obvious clustering.

Lymphadenopathy occurred in six (2%) and parotitis in three (1%) of the children who received the combined vaccine and none of the children who received the measles vaccine Two children developed appreciable bilateral parotitis associated with fever, irritability, and anorexia. One child developed these symptoms six hours after immunisation and the other 24 days after immunisation. Throat swabs were taken from both of these children and mumps virus was grown from both. The incidence of local reactions for both vaccines was low (5–7%); none of these were severe. One febrile convulsion occurred on the ninth day in a child who had received the combined vaccine. One child died four weeks after immunisation with the combined vaccine after an accident that was totally unrelated to the vaccine.

Discussion

When considering the introduction of a vaccine it is vital that it has been shown to be effective and to have no severe adverse reactions in the population to which it is to be given. Previous studies have examined the measles, mumps, and rubella vaccine in the United States and in Scandinavia,[11–15] but this is the first study in Britain, and an early study with the Merieux vaccine.

Careful consideration was given to a randomised and double blind study. It was finally decided that many parents would not accept randomisation and not knowing the type of vaccine that had been given to their child, and this would make recruitment difficult and selective. It is appreciated that the results of the clinical reactions might be affected by the parents' choice of vaccine, but the detailed diaries were intended to minimise this possible source of bias. The serological reponses could not have been affected by the open design It has been previously shown that seroconversion produced by the combined measles, mumps, and rubella vaccine is as good as the seroconversion produced by each of the single components.[16] This trial confirms this for the measles part of the Merieux vaccine. The seroconversion rates for the measles, mumps, and rubella vaccine are comparable with those of other studies.[12–15]

The overall incidence of signs and symptoms recorded in the three weeks after immunisation was very high in both vaccine groups, causing initial concern. These results can probably be partly explained by the fact that parents recorded all symptoms and signs in the diaries which produced sensitive but not very specific results. Another explanation for the high incidence of symptoms is that children of this age are suffering from many minor coincidental illnessess. Similar results have been found by Vesikari *et al* [14] They realised that their figures did not indicate an absolute incidence of reactions to the vaccine because there was no placebo group to act as a control. This trial also contained no placebo group, but the measles vaccine group acted as a control. The incidence of reactions from the measles, mumps, and rubella vaccine has been well demonstrated by Peltola and Heinonen in a placebo controlled twin study.[17] They found the actual incidence of reactions to be very low and some symptoms had a higher incidence in the placebo group. In our study the clustering of symptoms of fever, rash, and irritability at the end of the second week matches the well recorded pattern of reaction to the measles vaccine. We have shown that there is no significant difference in reactions between the measles, mumps, and rubella vaccine and the single measles vaccine, which is already widely accepted in this country

Two children developed considerable parotitis, associated with fever, anorexia, and irritability and mumps virus was isolated from their throat swabs Both children had high mumps titres postimmunisation The abnormal timing of the symptoms in relation to the immunisation suggested that they were more likely to be due to a coincidental mumps infection. Typing of the virus, however, did not differentiate between the wild and the vaccine strains.

Oxfordshire has some of the highest immunisation rates in the country and the parental response to this trial may not be representative of the whole country. It is encouraging, however, that 29% of the parents approached were willing for their children to be given the measles, mumps, and rubella vaccine as part of a trial which concerned a new vaccine and two venepunctures. During the explanation to obtain assent to the study the parents seemed to understand the purpose of vaccinating young children against measles, mumps, and rubella. This suggests that the introduction of the combined vaccine will be acceptable to parents. It is hoped that an effective campaign to introduce the combined vaccine would make it popular and would also boost the present immunisation rates against measles. When the vaccine is introduced health visitors will play a vital part in ensuring the understanding and acceptance of it among parents.

As part of this trial health visitors in the area were informed about the measles, mumps, and rubella vaccine. In follow up survey of 106 health visitors, 98 (92%) of them thought that the vaccine should be introduced

We have shown that this measles, mumps, and rubella vaccine produces an adequate serological response in children aged 13 months and produces no more clinical reactions than measles vaccine alone. We eagerly await the start of the national programme and decisions on the questions of a booster at the age of about 12 years and on the appropriate health education for parents and health service staff.

We would like to thank all the members of the department of community medicine and paediatrics who helped with the study In particular, we thank Sandy Pitt for her work Laboratory support was provided by the virology department We also thank the health visitors and the general practitioners for their support and all the parents who took part in this study for their cooperation

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17OH-progesterone rhythms in congenital adrenal hyperplasia

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SUMMARY Serial blood spot and saliva samples were collected at home by 18 patients being treated for congenital adrenal hyperplasia to determine the circadian rhythm of 17OH-progesterone as an index of therapeutic control. There was a strong correlation between the magnitude of the circadian fall and a single morning measurement of the plasma testosterone concentration taken near the time of the 17OH-progesterone rhythm samples. Poor control in pubertal girls produced an exaggerated circadian fall in 17OH-progesterone concentrations that were raised at all sampling times. Optimal control (plasma testosterone 1·5–2·5 nmol/l) was associated with blood spot and salivary 17OH-progesterone concentrations at 0800 hours of between 30–70 nmol/l and 260–1000 pmol/l, respectively, falling thereafter to <10 nmol/l and <150 pmol/l, respectively. Similar results were obtained in prepubertal patients. Nomograms have been constructed to interpret the daily profiles of blood spot or salivary measurements of 17OH-progesterone, or both. The analysis of 17OH-progesterone circadian rhythms is useful in monitoring treatment in patients with congenital adrenal hyperplasia, particularly those who may be overtreated.

Congenital adrenal hyperplasia is an uncommon disorder that is easily treatable with maintenance courses of steriods [1] The aim is to supplement the decreased production of adrenal cortisol with sufficient oral glucocorticoid to suppress excessive androgen secretion and yet permit normal growth and reproduction.[2–4] This is difficult to achieve for several reasons; though the normal rate of endogenous cortisol production is known,[5] there is considerable individual variation in the dose of glucocorticoid required to achieve adequate replacement.[2 3 6] Glucocorticoid preparations vary in their duration of action and there is uncertainty about their potency in congenital adrenal hyperplasia.[3 6] The daily dosage regimen is also important.[7] Glucocorticoids have a narrow therapeutic range so overtreatment readily leads to signs of hypercortisolism. Conversely, undertreatment leads to signs of androgen excess. Both options may ultimately result in diminished adult height.[4 7] Clinical indices of control such as growth and pubertal development must be monitored; they change slowly in reponse to alterations in treatment, however, and the effects of inadequate treatment may be irreversible.

Many biochemical indices have been used,[8–12] but control often remains suboptimal. The value of single random measurements of 17OH-progesterone is limited because of the circadian rhythm in the secretion of this steroid.[13 14] Further methods to refine control are needed.

The results of a previous study suggested that the shape of the 17OH-progesterone rhythm may be associated with the degree of therapeutic control.[6] This paper reports the results of the use of multiple blood spot and salivary 17OH-progesterone measurements and the results were compared with plasma testosterone measurements, a reliable index of androgen production.

Patients and methods

Twenty patients aged from 2·5 to 20 years, of whom 15 were female, with congenital adrenal hyperplasia due to 21-hydroxylase deficiency provided data for the study Blood spot or salivary 17OH-progesterone profiles, or both, were accumulated over a three year period from home collection of samples of capillary blood and saliva at 0800, 1200, 1800, and 2200 hours, usually on two consecutive weekend days. Blood spots were obtained using an Autolet device and collected onto Guthrie cards that were stored at 4°C until transferred to the laboratory. A profile represents 17OH-progesterone concentrations during one day. The dose of glucocorticoid, given either as hydrocortisone in divided doses or as dexamethasone once daily, was adjusted according to clinical indices of control, as well as single random measurements of plasma 17OH-progesterone and testosterone concentrations, and where appropriate, plasma renin activity. Profiles of 17OH-progesterone in two pubertal male patients were excluded from the analysis because of predominant testicular testosterone production at this age. The remaining 12 pubertal female patients and six prepubertal children provided a total of 80 blood spot, and 127 saliva profiles for analysis. Data from several additional incomplete profiles were also included in the analysis where appropriate.

Plasma and salivary 17OH-progesterone,[15] blood spot 17OH-progesterone,[16] and plasma testosterone[17] concentrations were determined by radioimmunoassay. The results were analysed by non-parametric statistical methods as the data were generally not normally distributed. Methods are stated where appropriate. The descriptive statistics of median and centiles were used as measures of location and scatter, rather than mean and standard deviation. The magnitude of the 17OH-progesterone circadian rhythm was calculated as the difference between the maximum and minimum 17OH-progesterone concentrations during the day, and was termed the peak trough fall. The result of each 17OH-progesterone profile was compared with the plasma testosterone concentration that had been measured in a morning blood sample collected in clinic held three days after the weekend samples had been collected for measurement of 17OH-progesterone concentrations. Data from pubertal female patients and prepubertal children were analysed separately according to the normal testosterone values for these ages—that is 0·3–2·5 nmol/l and <0·5 nmol/l, respectively.[13-20]

Results

All 20 patients showed a circadian rhythm in blood spot and salivary 17OH-progesterone concentrations. There was a morning peak and an evening trough that were consistent for each patient on consecutive weekend days. Figures 1 and 2 show the profiles of 17OH-progesterone in blood spot and salivary samples in relation to three defined ranges of plasma testosterone concentration: 0·3–2·5 nmol/l (normal range for pubertal female patients), 2·6–5·9 nmol/l (moderately raised and indicating poor control), and >6 nmol/l (severely raised and indicating extremely poor control). The results of the 17OH-

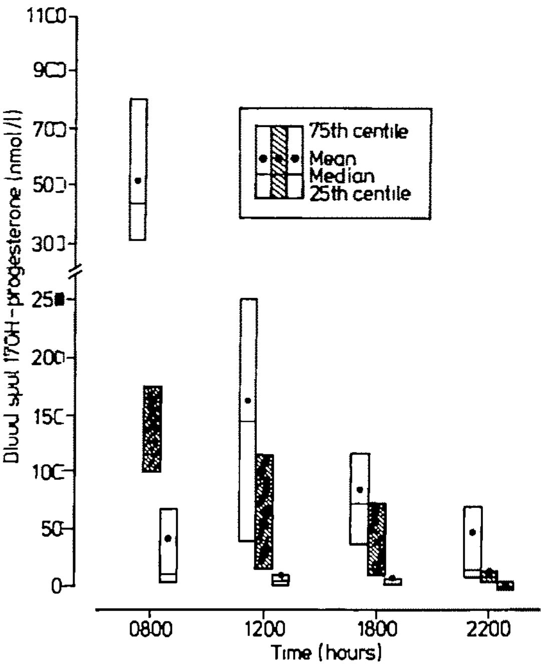

Fig 1 *Blood spot 17OH-progesterone concentrations and sampling times classified according to range of plasma testosterone concentrations determined in single morning blood sample. Open bars denote testosterone >6·0 nmol/l, cross hatched bars 2·6–5·9, and shaded bars 0·3–2·5 nmol/l.*

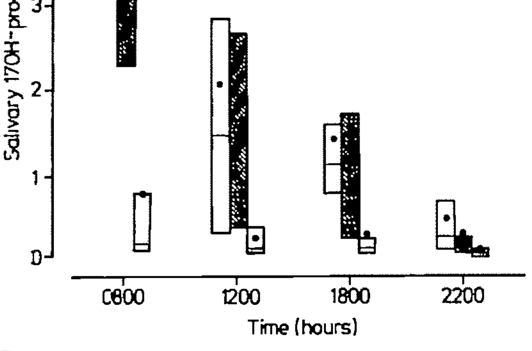

Fig 2 *Salivary 17OH-progesterone concentration sampling time, and plasma testosterone range.*

Table 1 *Blood spot and salivary 17OH-progesterone concentrations, sample times, and plasma testosterone concentrations in pubertal girls*

	Sampling time (hours)											
	0800			*1200*			*1800*			*2200*		
	T1	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*
Blood spot (nmol/l)												
No of observations	16	12	15	14	12	15	15	12	15	15	11	15
Mean	525	140	42	162	67	12	86	40	9	50	10	4
Median	436	115	10	145	56	5	76	17	5	17	10	3
25th centile	312	100	3	40	15	2	38	11	3	10	7	2
75th centile	811	177	69	253	114	10	118	74	7	71	15	5
Saliva (pmol/l)·												
No of observations	16	37	30	16	36	30	15	21	25	16	32	28
Mean	7985	3591	798	2079	1783	287	1439	1387	308	482	308	110
Median	5837	3310	210	1523	1478	133	1120	450	140	285	184	100
25th centile	4725	2324	131	345	415	100	823	275	82	137	115	54
75th centile	11031	4690	820	2895	2635	392	1620	1752	262	700	303	136

Plasma testosterone (nmol/l) ranges T1, >6·0, T2, 2·6–5 9, T3, 0 3–2 5

progesterone measurements have been expressed as mean, median, and interquartile range (25th–75th centiles) (table 1). Blood spot and salivary 17OH-progesterone concentrations in all three groups fell throughout the day being at their lowest by 2200 hours. There was a clear separation between the 17OH-progesterone concentrations at each sampling time and for each range of testosterone concentrations. High plasma testosterone concentrations were associated with increased blood spot and salivary 17OH-progesterone concentrations ($p<0.001$ using the Kruskal-Wallis one way analysis of variance). Patients with testosterone concentrations within the normal range were clearly separated from the other two groups. Maximum separation occurred when sampling was performed at 0800 hours.

Figures 3 and 4 show the association between peak trough fall and plasma testosterone concentra-

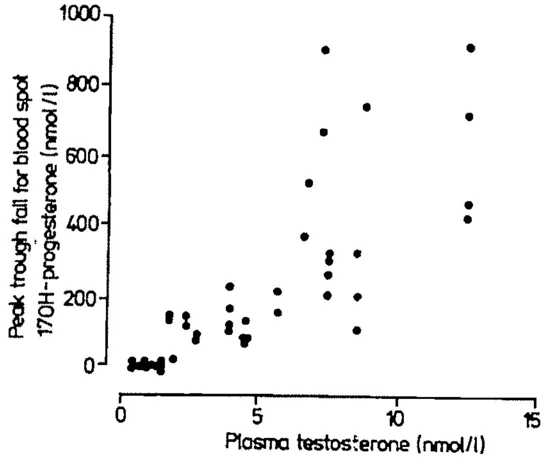

Fig 3 *Peak trough fall in blood spot 17OH-progesterone concentrations and plasma testosterone concentrations.*

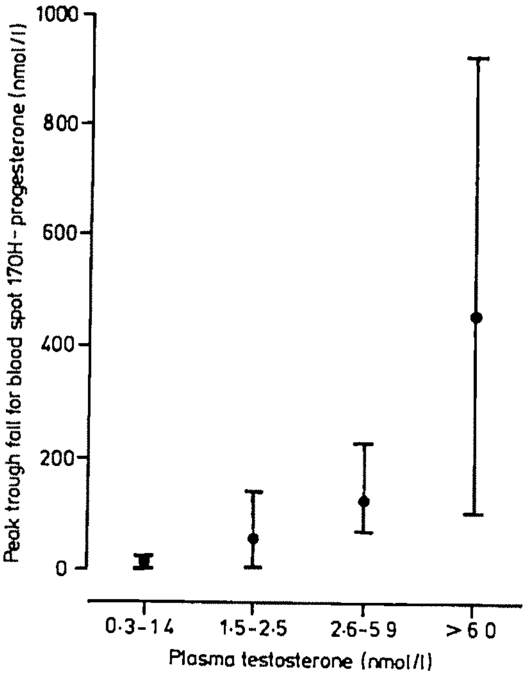

Fig 4 *Peak trough fall for blood spot 17OH-progesterone values and four ranges of plasma testosterone concentrations Means, maxima, and minima shown*

Table 2 *Blood spot and salivary 17OH-progesterone measurements that differentiate the degree of control in treated congenital adrenal hyperplasia at each sampling time*

Degree of control	Plasma testosterone concentration (nmol/l)	17OH-progesterone concentrations							
		0800 hours		1200 hours		1800 hours		2200 hours	
		Blood spot	Saliva	Blood spot	Saliva	Blood spot	Saliva	Blood spot	Saliva
Good	0·3–2·5	<70	<1000	<12	<130	<8	<160	<7	<130
Poor	2·6–5·9	70– 240	1000– 4700	12– 144	130– 4300	8– 115	160– 4500	7– 18	130– 800
Extremely Poor	>6·0	>240	>4700	>40	>400	>18	>270	>10	>250

Blood spot 17OH-progesterone (nmol/l), saliva 17OH-progesterone (pmol/l).

tions. There was a positive correlation indicating that increased testosterone values were associated with a pronounced fall in blood spot 17OH-progesterone concentrations throughout the day. (Spearman's correlation coefficient, r=0·85, p<0·001). There was a negligible 17OH-progesterone circadian rhythm when plasma testosterone concentrations were low. Similar results were obtained when salivary 17OH-progesterone profiles were analysed (unpublished).

Analysis of individual 17OH-progesterone values, their ranges, and centile distributions, allowed selection of values for each sampling time that differentiated between the three groups of patients Table 2 shows the results, which are represented as nomograms in figs 5 and 6. The blood spot and salivary 17OH-progesterone concentrations at 0800 hours were less than 70 nmol/l and 1000 pmol/l,

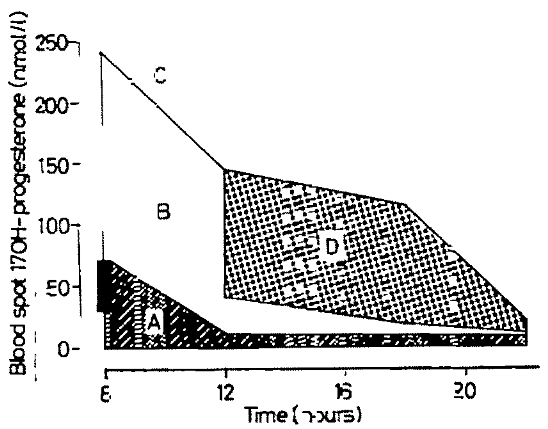

Fig 5 *Nomogram to monitor control in congenital adrenal hyperplasia using blood spot 17OH-progesterone profiles Labelled areas indicate A good control; B: poor control, C extremely poor control, D. area where areas B and C overlap The shaded bar denotes a 17OH-progesterone range of 30–70 nmol/l at 0800 hours which avoids overtreatment*

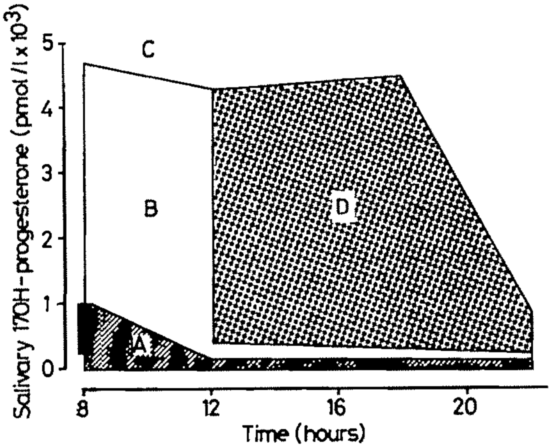

Fig 6 *Nomogram to monitor control in congenital adrenal hyperplasia using salivary 17OH-progesterone profiles The shaded bar denotes a 17OH-progesterone range of 260–1000 pmol/l at 0800 hours. A good control; B poor control, C extremely poor control, D area where values from B and C overlap.*

respectively, when daily 17OH-progesterone profiles were associated with plasma testosterone concentrations between 0·3 and 2·5 nmol/l Corresponding values at 1200, 1800, and 2200 hours for blood spot 17OH-progesterone (salivary 17OH-progesterone) were: <12 (130), <8 (160), and <7 (130). Some of these profiles were found in patients with clinical signs of hypercortisolism. Their 17OH-progesterone rhythms were characteristically suppressed or completely abolished together with low peak trough falls. The corresponding testosterone concentrations were significantly lower (<1·5 nmol/l) than in patients treated adequately (p<0·01, Mann-Whitney U test). The differences between the two treatment groups are shown in table 3 and fig 4. Profiles of 17OH-progesterone with 0800 hour values in the range 30–70 nmol/l in blood spots and 260–1000 pmol/l in saliva, decreasing thereafter into the ranges <10 nmol/l and <150 pmol/l, respec-

Table 3 *Comparison of 17OH-progesterone profiles and testosterone ranges in over and adequately treated patients*

Degree of control	*17OH-progesterone profiles*	*Peak trough fall*		*Plasma testosterone (nmol/l)*	
		Mean	*Range*	*Mean*	*Range*
Overtreated	Blood spot (n=10)	3	1–16	1·1	0·3–1·4
	Saliva (n=23)	283	—	1·1	0·3–1·4
Adequately treated	Blood spot (n=5)	111	18–112	2·1	1·5–2·5
	Saliva (n=8)	1888	—	2·0	1·5–2·5

Peak trough fall nmol/l (blood spot), pmol/l (saliva)

tively, indicated by shading and marked 'A' on the nomogram, were associated with plasma testosterone concentrations within the upper part of the normal range for pubertal girls, and no clinical signs of hypercortisolism. Profiles with values below these ranges were associated with overtreatment, despite apparently normal plasma testosterone concentrations.

Five prepubertal patients provided 27 blood spot and 19 salivary 17OH-progesterone profiles for analysis. Only six 17OH-progesterone profiles (three blood spot and three salivary) were associated with normal plasma testosterone concentrations (<0·5 nmol/l). Figure 7 shows the relationship between peak trough fall and plasma testosterone concentrations in prepubertal patients; there was a significant positive correlation between the two indices (Pearson's correlation r = 0·63, p<0·001). Similar results were obtained when salivary 17OH-progesterone profiles were analysed (unpublished data). Figure 7 shows that children with plasma testosterone concentrations of >0·5 nmol/l had peak trough fall values above 60 nmol/l (1000 pmol/l when saliva profiles were analysed). These were similar to the peak trough fall values that indicated poor control in pubertal girls (see figs 5 and 6). Consequently the nomograms may be used to interpret 17OH-progesterone profiles in prepubertal children though only the two categories of 'good' and 'poor' control can be distinguished.

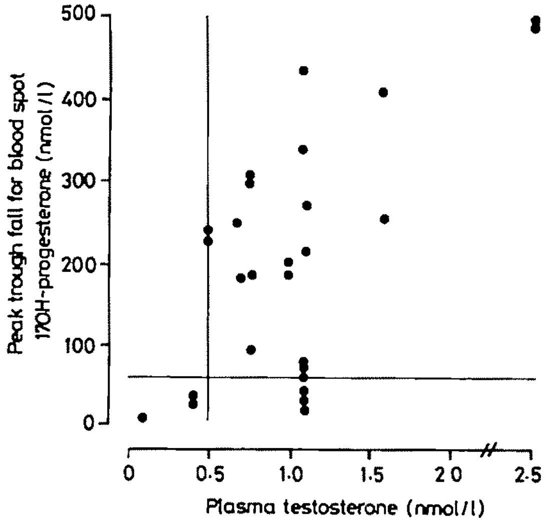

Fig 7 *Peak trough fall for blood spot 17OH-progesterone values and plasma testosterone concentrations in prepubertal children Vertical line indicates plasma testosterone concentration of 0·5 nmol/l, horizontal line peak trough fall value of 60 nmol/l.*

Discussion

The circadian rhythm in 17OH-progesterone secretion has been shown in plasma, blood spot, and salivary samples Concentrations of 17OH-progesterone were obviously raised in untreated patients with congenital adrenal hyperplasia patients and the circadian rhythm was still maintained.[21] The rhythm persists after glucocorticoid treatment is started but the magnitude varies according to the degree of therapeutic control In previous reports the difficulty of using a single, random measurement of 17OH-progesterone as an index of control in congenital adrenal hyperplasia has been emphasised.[4 8 10–12]

Single measurements of plasma testosterone are often used to monitor control in congenital adrenal hyperplasia. They are of limited use as an index of overtreatment because of difficulties with the assay when there are low plasma and salivary concentrations. The predominance of testicular testosterone production in infant and pubertal male patients[3] further reduces the value of plasma testosterone as a marker of control in congenital adrenal hyperplasia. There is a circadian variation in testosterone values in normal subjects[22] and in patients with congenital adrenal hyperplasia,[14] though concentrations do not fluctuate as widely as those of 17OH-progesterone.

Increased plasma testosterone concentrations in pubertal girls were associated with wide fluctuations in 17OH-progesterone concentrations (expressed in this study as the peak trough fall). It was possible from this analysis to define well, poorly, and extremely poorly controlled patients. Similar analysis of the results from prepubertal children defined two groups who were well and poorly controlled. A 17OH-progesterone circadian rhythm occurs in normal individuals, untreated patients with congenital adrenal hyperplasia, and treated patients. The rhythm is abolished by excessive glucocorticoid treatment in patients with congenital adrenal hyperplasia The use of 17OH-progesterone profiles provides an accurate index of therapeutic control, and in particular highlights overtreatment with a sensitivity previously unattainable in the management of congenital adrenal hyperplasia.[3] Signs of hypercortisolism apppear when treatment is designed to achieve 17OH-progesterone concentrations within the range for normal individuals.[2] Profiles of 17OH-progesterone obtained from two pubertal male patients during this study showed a similar pattern to that observed in pubertal girls and children. The method may be useful in monitoring control in this group of patients with congenital adrenal hyperplasia

Measurement of 17OH-progesterone is a rapid and reliable test for the diagnosis of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency.[4 8 10] The test has been less acceptable as a reliable marker of control in congenital adrenal hyperplasia.[4 8 10-12] Previous studies, however, did not analyse the 17OH-progesterone circadian rhythm in patients with congenital adrenal hyperplasia in association with varying degrees of therapeutic control. It is now possible to define all categories of control by reference to the 17OH-progesterone nomograms described here. Prospective analysis of 17OH-progesterone profiles determined in blood spot and salivary samples shows more than 80% accuracy in predicting a plasma testosterone value by reference to the nomograms. Inaccurate prediction in the remainder was associated only with the degree of poor control

Single measurements of 17OH-progesterone have commonly been used to monitor treatment in congenital adrenal hyperplasia This study clearly shows how the practice can provide misleading results. There was an overlap in 17OH-progesterone values during the afternoons and evenings in all groups of patients studied (figs 1 and 2). Even a single 17OH-progesterone measurement at 0800 hours may be misleading because some patients may show loss of control only during the latter part of the day. Techniques are now available that determine 17OH-progesterone profiles by serial collection of either blood spot or salivary samples Each type is easy to collect from children. Salivary sampling can be time consuming in infants and is generally disliked by adolescent girls. The use of the 17OH-progesterone nomograms now allows fine adjustment to the individual treatment of congenital adrenal hyperplasia at all ages.

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Androstenedione rhythms in saliva in congenital adrenal hyperplasia

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SUMMARY Serial samples of saliva were collected at home by 17 patients being treated for congenital adrenal hyperplasia to determine the circadian rhythm of androstenedione as an index of therapeutic control. Single samples of blood for measurement of plasma testosterone, 17OH-progesterone, and androstenedione concentrations were collected from these and a further seven patients for comparison. Plasma androstenedione concentrations showed a close correlation with plasma concentrations of 17OH-progesterone and testosterone. There was a strong correlation between the salivary androstenedione profiles and plasma testosterone concentrations in pubertal girls. Concentrations of androstenedione in saliva decreased during the day but remained raised at each sampling time in relation to plasma testosterone concentrations. Salivary androstenedione profiles are shown as nomograms to distinguish the degree of therapeutic control. The concentration of androstenedione, measured in plasma or saliva, is an alternative marker to monitor control of treatment in congenital adrenal hyperplasia. The measurement in saliva is a useful index of androgen production when blood sampling is difficult.

Measurements of 17OH-progesterone in blood spot and saliva are useful to monitor treatment in patients with congenital adrenal hyperplasia.[1] The measurement of plasma androstenedione concentrations has also been suggested.[2] Androstenedione is a weak adrenal androgen and, unlike 17OH-progesterone, single measurements are less affected by wide circadian variations in plasma concentrations.

This study reports the use of salivary androstenedione profiles to monitor treatment in congenital adrenal hyperplasia. The results are compared with single random measurements of plasma androstenedione, testosterone, and 17OH-progesterone as indices of the degree of control.

Patients and methods

Twenty four patients aged 2 to 22 years with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, provided data for the study. Androstenedione profiles were measured in 17 patients 11 of whom were female over a two year period. Samples of saliva were collected at home at 0800, 1200, 1800, and 2200 hours, on two consecutive weekend days. A profile represents androstenedione concentrations during one day. The dose of glucocorticoid, given either as hydrocortisone in divided doses or as dexamethasone once daily, was adjusted according to clinical indices of control, and single random measurements of plasma 17OH-progesterone, testosterone, androstenedione concentrations, and where appropriate, plasma renin activity. Androstenedione profiles in two pubertal male patients were excluded from the analysis because of predominant testicular production at this age. The remaining 11 pubertal female patients and four prepubertal children provided a total of 44 profiles (28 and 16, respectively) for analysis. Data from an additional 11 incomplete profiles were also included in the analysis where appropriate.

The result of each salivary androstenedione profile was compared with the plasma testosterone concentration that had been measured in a morning blood sample collected at a recent clinic. Data from pubertal female patients and prepubertal children were analysed separately according to the normal testosterone values for these ages—that is, 0·3–2·5 nmol/l and <0·5 nmol/l, respectively.[2–4]

Plasma testosterone,[5] plasma 17OH-progesterone[6] and plasma and salivary androstenedione[7] concentrations were measured by radioimmunoassay. The results were analysed by non-parametric statistical methods as the data were generally not normally distributed. The methods are stated where appropriate

Results

Fig 1 shows the association between simultaneous measurements of plasma androstenedione and testosterone concentrations in patients with treated congenital adrenal hyperplasia. There was a strong correlation ($r=0{\cdot}9$, $p<0{\cdot}001$), with values being lowest in prepubertal children Fig 2 shows a similar correlation between plasma androstenedione and 17OH-progesterone concentrations ($r=0{\cdot}8$, $p<0{\cdot}001$)

There was a circadian variation in salivary androstenedione concentrations in all 17 patients who provided profiles. The concentration of androstenedione at 0800 hours was usually greater than .

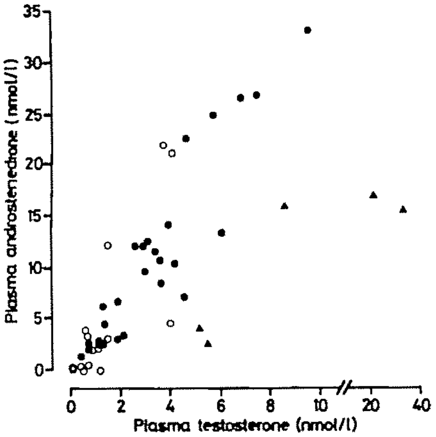

Fig 1 *Association between simultaneous measurements of plasma androstenedione and testosterone concentrations in patients being treated for congenital adrenal hyperplasia O=prepubertal patients (n=7), ●=pubertal female patients (n=13), and ▲=pubertal male patients (n=3)*

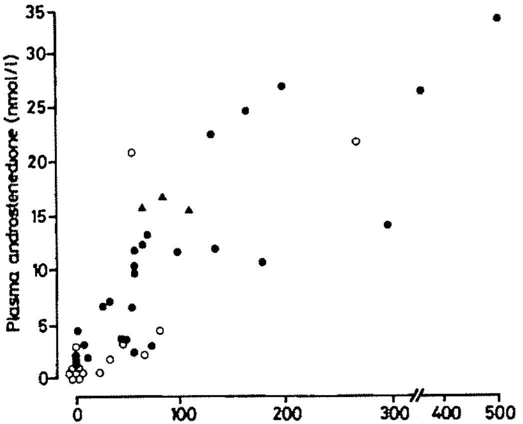

Fig 2 *Association between simultaneous measurements of plasma androstenedione and plasma 17OH-progesterone in patients being treated for congenital adrenal hyperplasia; O=prepubertal patients (n=7); ●=pubertal female patients (n=13); and ▲=pubertal male patients (n=3)*

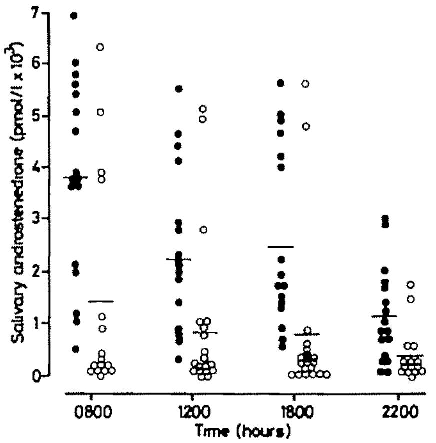

Fig 3 *Concentrations of androstenedione in saliva in relation to sampling time and range of plasma testosterone concentrations Bars=mean values; ●=plasma testosterone >2·5 nmol/l; and O=plasma testosterone <2·5 nmol/l*

Table 1 *Salivary androstenedione and plasma testosterone concentrations in pubertal females*

	Sampling time (hours)							
	0800		*1200*		*1800*		*2200*	
	**T1*	*T2*	*T1*	*T2*	*T1*	*T2*	*T1*	*T2*
No of observations	17	16	17	21	18	20	17	19
Salivary androstenedione (pmol/l)								
Mean	3836	1460	2344	839	2484	804	1145	429
Range	540–6900	69–6309	330–5500	66–5112	583–5600	82–5628	80–3000	61–1823

*T1—plasma testosterone concentration >2 5 nmol/l, T2—plasma testosterone concentration <2 5 nmol/l that at 2200 hours, but a consistent fall in androstenedione concentrations at each sampling time was seen in only one third of the profiles. Fig 3 and table 1 show the results of salivary androstenedione profiles in pubertal female patients. The profiles were subdivided according to testosterone values greater or less than 2·5 nmol/l. Salivary androstenedione values in both groups gradually fell during the day to their lowest values at 2200 hours. Increased plasma testosterone concentrations were generally associated with high salivary androstenedione concentrations at each sampling time. Although there was some overlap in androstenedione values in the two groups, mean salivary androstenedione concentrations were significantly higher at all sampling times in those patients with plasma testosterone values greater than 2·5 nmol/l (p<0·001, Mann-Whitney U test). The positive correlation between salivary androstenedione values at 2200 hours and plasma testosterone concentrations is shown in Fig 4. A similar association was seen at each sampling time (table 2). The results may be used to derive values for salivary androstenedione concentrations that distinguish patients with normal or raised plasma testosterone concentrations. The nomogram (fig 5) indicates how salivary androstenedione profiles may be used to monitor the adequacy of treatment in pubertal females with congenital adrenal hyperplasia.

Salivary androstenedione profiles were available for analysis in only four prepubertal children. There was a correlation between salivary androstenedione and plasma testosterone concentrations at every sampling time except 1200 hours (table 3 and fig 6). Fig 7 and table 3 show how salivary androstenedione profiles can distinguish adequate from poor control

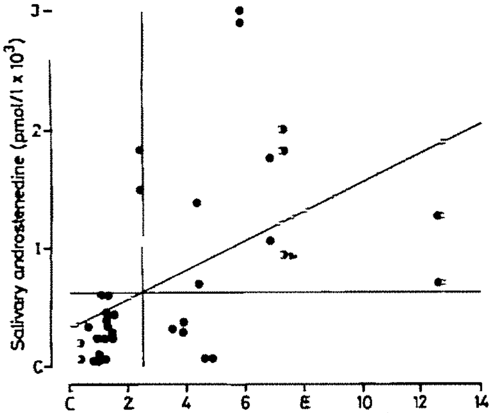

Fig 4 *Association between salivary androstenedione concentrations and plasma testosterone in pubertal female patients at 2200 hours. Vertical line denotes plasma testosterone concentration of 2·5 nmol/l, and horizontal intersection of this and regression line denotes androstenedione concentration in saliva that distinguishes good and poor control.*

Table 2 *Salivary androstenedione concentrations that differentiate the degree of control in pubertal female patients at each sampling time according to plasma testosterone concentration of 2·5 nmol/l*

	Sampling time (hours)			
	0800 (n=33)	*1200 (n=38)*	*1800 (n=38)*	*2200 (n=36)*
Spearman's rank correlation coefficient (r)	0·70	0·71	0·78	0·70
p Value	<0·001	<0·001	<0·001	<0·001
Androstenedione concentration (pmol/l)	2150	1270	1300	6[illegible]0

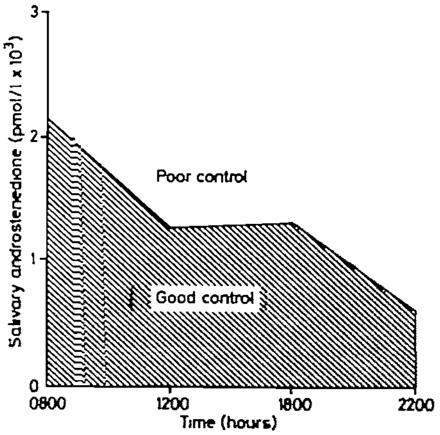

Fig 5 *Nomogram to monitor control in pubertal female patients with congenital adrenal hyperplasia using androstenedione profiles in saliva Area labelled "good control" is associated with plasma testosterone concentrations within normal range of 0·3–2·5 nmol/l*

Table 3 *Salivary androstenedione concentrations that differentiate the degree of control in prepubertal children at each sampling time according to plasma testosterone concentration of 0·5 nmol/l*

	Sampling time (hours)			
	0800 (n=15)	*1200 (n=16)*	*1800 (n=16)*	*2200 (n=13)*
Spearman's rank correlation coefficient (r)	0·78	0·36	0·85	0·7[illegible]
p Value	<0·001	NS	<0·0001	<0·001
Androstenedione concentration (pmol/l)	1500	760	640	260

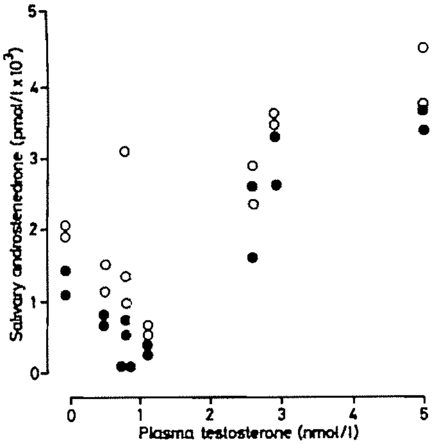

Fig 6 *Association between saliva androstenedione concentrations at 0800 hours (○) and 1800 hours (●) and plasma testosterone concentrations in prepubertal children*

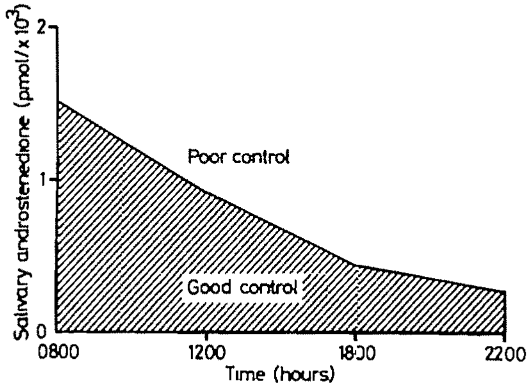

Fig 7 *Nomogram to monitor control in prepubertal children with congenital adrenal hyperplasia using androstenedione profiles in saliva. Area labelled "good control" is associated with plasma testosterone concentrations of less than 0·5 nmol/l.*

in prepubertal children with congenital adrenal hyperplasia.

Discussion

Single, random measurements of steroids, particularly 170H-progesterone, can be difficult to interpret when used to monitor treatment of congenital adrenal hyperplasia. Testosterone has been used most frequently as a single marker but in infant and pubertal male patients the concentration of steroid reflects testicular rather than adrenal androgen production. Measurement of plasma androstenedione concentration has been advocated as a useful alternative.[2] This study confirms the strong association between simultaneous measurements of plasma testosterone, androstenedione, and 170H-progesterone concentrations.[8] Korth-Schutz *et al*[2] reported that poor control of congenital adrenal hyperplasia was associated with increased plasma testosterone and androstenedione concentrations. They concluded that androstenedione concentrations were more accurate in distinguishing between patients in good and poor control

We have shown an association between salivary androstenedione and plasma testosterone concentrations. There was a circadian rhythm in androstenedione concentrations in treated patients with congenital adrenal hyperplasia irrespective of age, sex, or stage of puberty. The magnitude of the circadian rhythm was less than for 170H-progesterone[1] but the accuracy of the salivary androstenedione nomogram for predicting adequacy of control in pubertal girls was still 90%. The nomogram was less discriminant as only two groups (adequate and poor control) could be identified. Only a small number of profiles from prepubertal children were available for analysis. There was a positive correlation between salivary androstenedione and plasma testosterone concentrations at most sampling times. The nomogram (fig 7) provides only an approximate guide to the control of treatment until the values for salivary androstenedione that will distinguish degrees of control are more precisely defined.

Androstenedione is a weak androgen which is secreted by both the adrenal glands and the gonads Measurement of it in patients with congenital adrenal hyperplasia provides a useful marker of excessive adrenal androgen production, particularly in pubertal male patients Salivary androstenedione profiles show a circadian rhythm that is closely associated with plasma testosterone concentrations, particularly in pubertal female patients. The profiles may be used alone, or in conjunction with 170H-progesterone to monitor androgen production [1] When the profiles of both steroids are used it is possible to achieve a sensitive degree of control and an index of androgen production in those patients who are reluctant to have blood samples taken.

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Growth hormone releasing hormone or growth hormone treatment in growth hormone insufficiency?

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SUMMARY Sixteen prepubertal children who were insufficient for growth hormone were treated with growth hormone releasing hormone (GHRH) 1–40 and GHRH 1–29 for a mean time of nine months (range 6–12 months) with each peptide. Eleven children received GHRH 1–40 in four subcutaneous nocturnal pulses (dose 4–8 μg/kg/day) and eight (three of whom were also treated with GHRH 1–40) received GHRH 1–29 twice daily (dose 8–16 μg/kg/day). Altogether 73% of the children receiving GHRH 1–40 and 63% receiving GHRH 1–29 showed a growth response. Double the daily dose of GHRH 1–29 was required to obtain equivalent growth response to pulsatile GHRH 1–40. A significant linear correlation was shown between growth hormone secretion and height velocity on GHRH 1–40 but not on GHRH 1–29 and there was a significant correlation between plasma GHRH and serum growth hormone concentrations during GHRH 1–40 administration.

Response to conventional growth hormone treatment in a matched group of children was significantly better than the response after GHRH. A significant improvement in height velocity was observed in the children transferred to growth hormone replacement. Growth hormone remains the treatment of choice in growth hormone insufficiency. GHRH treatment may be of benefit in children with less severe growth hormone insufficiency in the presence of pulsatile endogenous growth hormone secretion.

Growth hormone secretion is controlled by inhibitory somatostatin and stimulatory growth hormone releasing hormone (GHRH).[1–3] In subjects with growth hormone sufficiency or insufficiency intravenous GHRH results in growth hormone release from the pituitary.[4–6] Preliminary reports indicate that GHRH may have a therapeutic role in the treatment of children who are growth hormone insufficient.[7–9] Evaluation of different treatment regimens, however, has been limited The aims of this study were to investigate the relation between GHRH administration and growth hormone secretion and the therapeutic effects of alternative modes of administration and dose regimens of GHRH in children with growth hormone insufficiency and to compare the linear growth response with conventional growth hormone replacement.

Patients and methods

Sixteen prepubertal children (11 boys, five girls) with bone ages of less than 10 years were recruited to the study between January 1985 and July 1986. The pretreatment clinical details are summarised in table 1. Auxological observation over a period of one year had shown a low growth velocity, and

Table 1 *Pretreatment clinical data (n=16)*

	Mean (SD)	*Range*
Age (years)	8·5 (2·2)	4·9 to 11·9
Bone age (TW2)	5·9 (2·1)	2·5 to 8·8
Height SDS	−2·4 (1·0)	−4·8 to −0·6
Height velocity (cm/year)	3·8 (0·9)	1·7 to 5·7
Height velocity SDS	−2·2 (0·8)	−4·1 to −0·9
Maximum growth hormone concentration (on insulin tolerance test) (mU/l)	6·5 (5·3)	1·9 to 17·0
Maximum growth hormone concentration (during sleep) (mU/l)	9·3 (5·7)	4·0 to 26·0
Sum % of 24 hour growth hormone pulse amplitude (mU/l)	27·0 (24·0)	4·0 to 93·0

hypothalamo pituitary assessment, using insulin induced hypoglycaemia with thyrotrophin releasing hormone and luteinising hormone releasing hormone stimulation, confirmed isolated growth hormone insufficiency in 10 children and multiple pituitary hormone deficiencies in six children. The children with multiple pituitary hormone deficiencies received appropriate hormonal replacement before GHRH, and pituitary hypoplasia was shown in all cases by high resolution computed tomography (GE 8800). One child had been treated with human growth hormone for four years but stopped treatment three months before starting GHRH. The remaining children had received no treatment for growth hormone insufficiency.

The studies were approved by the Middlesex Hospital Clinical Investigation Committee, the Department of Health and Social Security, and USA Food and Drugs Administration. Written parental consent was obtained.

Before starting GHRH a 24 hour endogenous growth hormone profile was obtained from each child by withdrawing blood samples (1 ml) every 20 minutes. Serum growth hormone profiles were also obtained throughout the study during each treatment regimen. An intravenous GHRH study (1 µg/kg) was performed before GHRH treatment and in 11 children at intervals of three months throughout the study (blood samples taken at −20, −10, 0, 2, 5, 10, 20, 30, and at 15 minute intervals up to 120 minutes).

During the GHRH 1–40 regimen profiles for plasma immunoreactive GHRH concentrations were obtained on each dose schedule in six children in conjunction with serum growth hormone estimations.

Anthropometric measurements were made every three months by the same observer using standard techniques, and bone age assessment was performed at the beginning of the study and after any change in treatment.[10 11] The measurements obtained were described as raw height velocity (cm/year) when assessing the short term (three month) results or as the standard deviation score (SDS) when assessing the overall results.[12]

GHRH TREATMENT

The first 11 children received GHRH 1–40 (supplied by Professor MO Thorner) by nocturnal pulsatile infusion every three hours for four pulses per night. A mini pump (Zyklomat, Ferring) delivered each pulse over one minute via a 27 gauge infusion needle inserted subcutaneously into the anterior abdominal wall. A dose of 1 µg/kg/pulse (4 µg/kg/day) was given for the first three months in six children followed by 2 µg/kg/pulse (8 µg/kg/day) for the rest of the study period. The remaining five children received the higher dose regimen throughout the GHRH 1–40 study period.

Eight children received GHRH 1–29 (KabiVitrum) subcutaneously into anterior abdominal wall in an initial dose of 4 µg/kg/dose (8 µg/kg/day) twice daily for three months followed by a dose of 8 µg/kg/dose (16 µg/kg/day) for the remaining treatment period. Three GHRH 1–40 'responders' were transferred directly to GHRH 1–29. The mean treatment duration on both GHRH peptides was nine months (range 6–12 months).

On completion of the GHRH study each child was transferred to somatrem (Somatonorm, KabiVitrum) in a dose of 2 IU growth hormone subcutaneously six times a week. The growth results (age, bone age, height SDS, height bone age SDS, and height velocity SDS) on GHRH were compared with a matched group of naive idiopathic insufficient children who received somatrem from January 1986 in an identical regimen.

GROWTH HORMONE ASSAY

Serum growth hormone concentration was assayed using a Tandem R human growth hormone immunoradiometric assay kit (Hybritech) with the standards calibrated against the National Institute of Health human growth hormone reference preparatin HS 2243E. The mean intra-assay coefficient of variation was 6·3% at 4·9 mU/l with an interassay coefficient of variation of 9·6%. All samples from the same sampling period were stored at −20C and assayed together.

GHRH 1–40 ASSAY

Plasma immunoreactive GHRH was assayed by radioimmunoassay using a specific rabbit GHRH 1–40 antiserum (NIBSC code No 84/591) as previously described.[13] Sensitivity of the assay was 10–20 pg/ml and at a dilution of 1 in 300 000 the antiserum bound 30–40% of freshly labelled GHRH. Intra-assay and interassay coefficients of variation were 6·5% and 9% respectively at a concentration of 400 pg/ml.

STATISTICS

Analysis of variance was used to compare the pretreatment characteristics of children receiving GHRH and growth hormone. Analysis of variance, multiple regression analysis, and Mann-Whitney U test were used to analyse the response to treatment.

Results

Both regimens were well tolerated with only one child experiencing slight stinging at the injection site

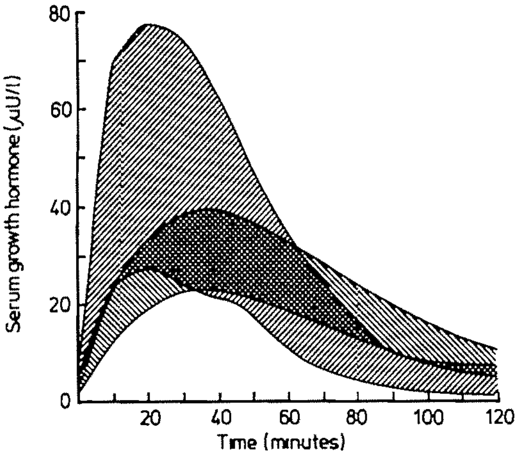

Fig 1 *95% Confidence limits after 1 μg/kg GHRH 1–40 given intravenously in growth hormone insufficient children* ▧ *and normal (adult) subjects* ▨

(GHRH 1–29). Most of the children in each group undertook their own injections under parental supervision (GHRH 1–40, nine children; GHRH 1–29, six children).

All children responded to intravenous GHRH (mean 31 mU/l; range 5·7–107) (fig 1). The response to intravenous GHRH was highly variable both between and within subjects throughout the study and there was no correlation with the growth response observed.[6] The 95% confidence limits of the growth hormone response to GHRH in normal adults and the study children is shown in fig 1. Within these limits there is no overlap in the two groups between GHRH administration and the first observed growth hormone response within 10 minutes of the study.

GHRH 1–40

All 11 children showed pulsatile GH secretion of growth hormone in response to nocturnal pulsatile GHRH administration from the first night of treatment. Eight of the 11 children had a significant growth response and maintained pulsatile growth hormone secretion throughout the study (fig 2). The growth velocity achieved reflected the dose regimens (table 2) with no significant improvement during the lower schedule A positive correlation was present between the stimulated growth hormone secretion and growth velocity ($r=0·78$; $p<0·001$; fig 3) and between the peak plasma immunoreactive GHRH concentrations obtained and the peak growth hormone secretion with each GHRH pulse ($r=0·75$; $p<0·001$, fig 4).

Three children failed to show a linear growth response to GHRH 1–40. In one child a diminishing growth hormone response with time was observed in association with a falling growth rate. In another child GHRH administration resulted in a high frequency growth hormone response which was

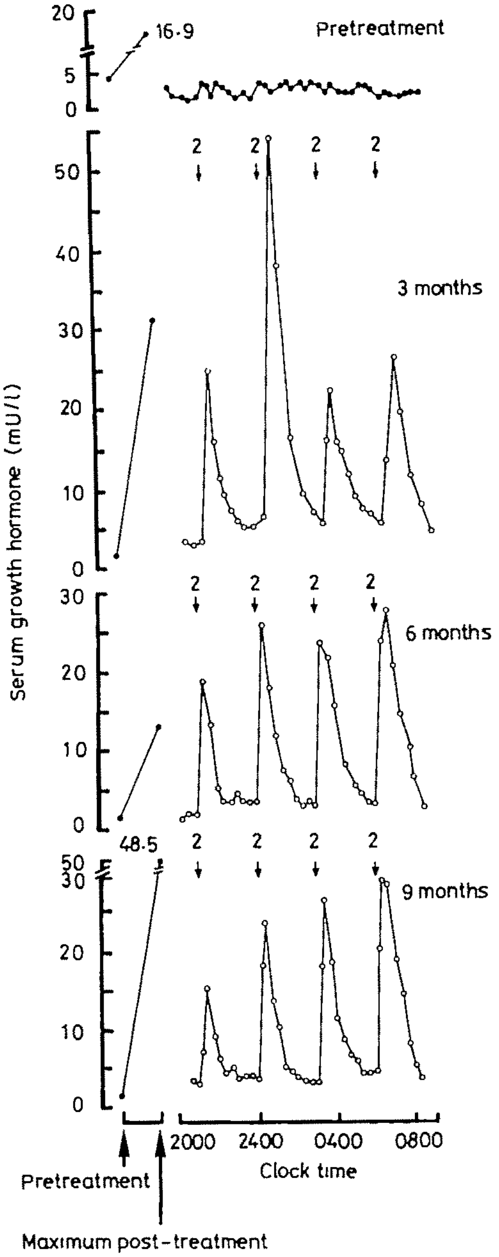

Fig 2 *Growth hormone response to subcutaneous GHRH 1–40 during treatment period 2 μg/kg/pulse in one child Responses to intravenous 1 μg/kg GHRH 1–40 are shown in the left panels*

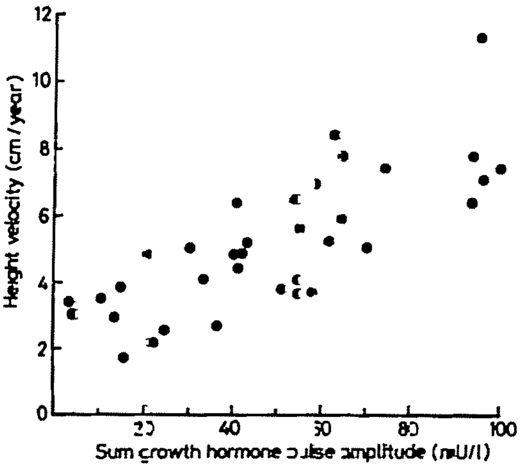

Fig 3 *Relation between growth hormone secretion and growth velocity on GHRH 1–40 (r=0·78, p<0·001)*

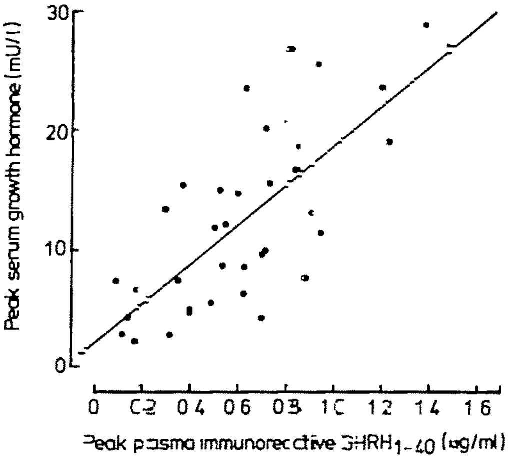

Fig 4 *Relation between peak GHRH and growth hormone concentrations during nocturnal pulsatile GHRH 1–40 (r=0·75, p<0·001)*

associated with no change in height velocity SDS and in a third inadequate growth hormone pulse amplitude (>15 mU/l) was achieved.

GHRH 1–29

The five naive patients and the three transfer patients showed pulsatile (two pulses) growth hormone secretion to twice daily GHRH 1–29 (fig 5). The higher growth hormone pulse amplitude observed after GHRH 1–29 in comparison with that after pulsatile GHRH 1–40 was not reflected in a more significant height velocity (table 2) Twice the daily dose of GHRH 1–29 was required to achieve equivalent growth responses. The relation between growth hormone secretion and velocity was only maintained by the transfer patients (transfer patients r=0·78, p<0·02; all GHRH 1–29 patients r=0·41, NS; 'naive' patients r=0·18, NS). Five children responded to GHRH 1–29 and the non-responders included two naive (one psychosocial, one noncompliance) and one transfer child (inadequate growth hormone secretion)

There was a highly significant increase in height velocity after GHRH 1–40 8 µg/kg/day and both GHRH 1–29 regimens (p<0·001), when compared with the preateatment height velocity, with no significant difference between the groups (table 2) When analysing the results of the 'responders' only there was a significant difference (p<0·01) between the height velocity on GHRH 1–40 8 µg/kg/day and GHRH 1–29 8 µg/kg/day (table 2).

GROWTH HORMONE TREATMENT

When comparing the change in height velocity SDS after GHRH with the change in height velocity SDS in the matched group of children receiving growth hormone there was a significant difference in the growth response observed (mean (SD) change in height velocity SDS; children on growth hormone +4·2 (1·9); children on GHRH +2·8 (2·3); p<0·04). The 10 GHRH treated children who have completed one year of somatrem treatment have shown a

Table 2 *Growth response to GHRH 1–40 and GHRH 1–29*

	Pretreatment	*GHRH 1–40*		*GHRH 1–29*	
		4 µg/kg/day	*8 µg/kg/day*	*8 µg/kg/day*	*16 µg/kg/day*
All patients	*(n=15)*	*(n=6)*	*(n=11)*	*(n=8)*	*(n=8)*
Mean (SEM) height velocity (cm/year)	3·8 (0·2)	4·5 (0·6)	6·4 (0·7)	5·1 (0·3)	5·9 (0·4)
Responders only		*(n=3)*	*(n=8)*	*(n=5)*	*(n=5)*
Mean (SEM) height velocity (cm/year)		5·1 (0·8)	7·6 (0·6)	5·5 (0·5)	6·5 (0·5)

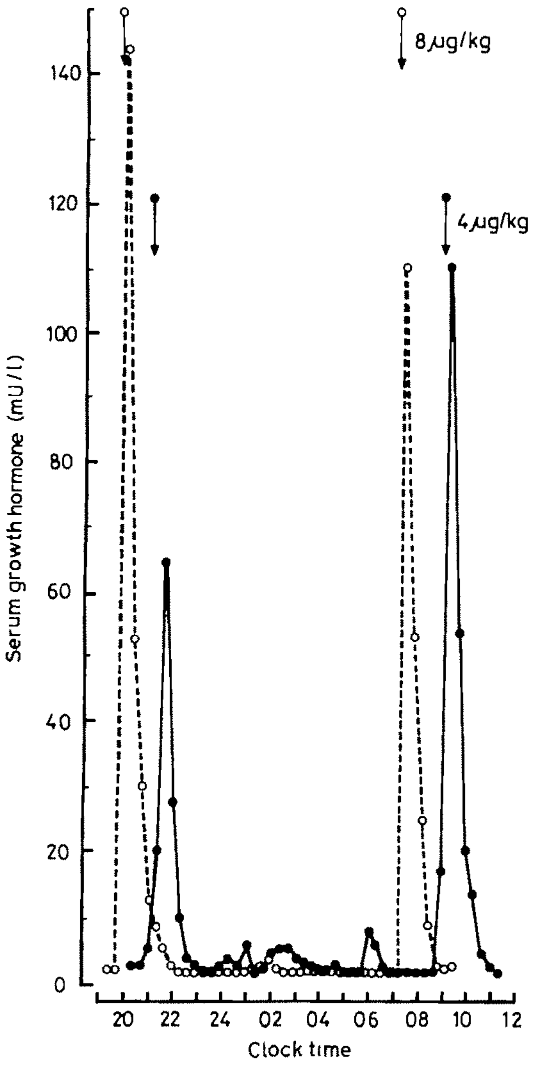

Fig 5 *Growth hormone response to GHRH 1–29 in two dose regimens in one child*

significantly greater growth response to pharmacological growth hormone replacement (mean (SD) height velocity: children on growth hormone 8·7 (2·5); children on GHRH 5·8 (2·0); $p<0·01$). In one child there was no difference in height velocity on either treatment and in another the height velocity was greater on GHRH.

Discussion

Intravenous administration of GHRH is capable of stimulating growth hormone release from the pituitary of subjects with growth hormone insufficiency.[4-5] To determine the therapeutic effect of GHRH in the treatment of growth hormone insufficiency different routes of administration, dose and frequency of GHRH administration, appropriate patient selection, and cost effectiveness of the regimen used require evaluation. The aim of this study was to investigate the relation of GHRH administration and growth hormone secretion and growth effect in growth hormone insufficient children.

The study was started at a time when growth hormone for therapeutic purposes was not available. Initially, an attempt was made to mimic (augment) physiological growth hormone secretion, an aim in which it was successful.[8] During the initial phase of the study a 1–29 analogue of the naturally occurring GHRH 1–40 became available and was used in some of the children to see if the growth they had achieved on GHRH 1–40 could be maintained on a twice daily regimen Contemporaneously, another study reported some success using this analogue and regimen[9] and we enrolled a further cohort of patients to evaluate its success in 'naive' patients who had not previously been treated in this manner. All patients subsequently were treated with growth hormone when the biosynthetic product became available.

All the children showed a growth hormone response to intravenous GHRH administration and the test was of no predictive value in determining the growth response to therapeutic GHRH administration. We used 95% confidence limits to compare the responses with those of normal subjects because of the highly variable responses observed in both normal and growth hormone insufficient subjects. The growth hormone peaks overlap between the groups but the lag between GHRH administration and the first observed growth hormone response was different within the first 10 minutes of the study. This difference would not have been apparent if the first blood sample after GHRH administration had been taken at 15 minutes as with previous studies.[4-5] More frequent sampling and further evaluation are required before the role of the dynamic GHRH study is determined in growth hormone insufficiency.

Altogether 75% of the children receiving nocturnal pulsatile GHRH 1–40 and 63% receiving GHRH 1–29 showed a significant change in height velocity SDS. A dose response relation was observed in the pulsatile study and was reflected in the relation between plasma GHRH and growth hormone concentrations as well as between the growth velocity and stimulated growth hormone secretion. A maximum dose response effect was observed in the GHRH 1–29 study with no difference in the growth response when the daily dose of GHRH 1–29 was doubled. The relation between stimulated growth hormone secretion and growth velocity was only maintained by the children who were transferred from the pulsatile regimen.

Methods of subcutaneous administration include intermittent injection, pulsatile or continuous infusion. Pulsatile GHRH administration was used initially to mimic endogenous pulsatile growth hormone secretion.[14] Thorner *et al* reported the successful treatment of two growth hormone insufficient children receiving pulsatile GHRH 1–40 every three hours throughout the 24 hours[7] Smith *et al* reported their initial findings in five children receiving nocturnal pulsatile GHRH 1–40[8] This study was to compare the growth response between different GHRH regimens and conventional growth hormone treatment.

Intermittent injection of GHRH has also been investigated by several groups. Hummelink *et al* concluded that a single daily injection of 10 μg/kg was inadequate to achieve a significant growth response.[15] Ross *et al* reported a 44% success rate after the administration of GHRH 1–29 twice daily in a dose of about 25 μg/kg/day[9] The growth response of their 'responders' was comparable with the results we found when we used one third of the daily dose of GHRH 1–40 administered in a pulsatile manner.

We recognise that the lack of prospective design strictly diminishes the scientific value of the therapeutic comparison we have made. Nevertheless the results do show that both GHRH regimens were capable of stimulating growth hormone secretion and an increased height velocity in growth hormone insufficient children. Pulsatile GHRH administration, stimulating a more normal pattern of growth hormone secretion, was by far the more cost effective both physiologically and pharmacologically.

Neither GHRH regimen, however, achieved comparable results with growth hormone treatment in either naive growth hormone insufficient children or in children transferred to growth hormone after study completion. Growth hormone treatment is the most appropriate treatment of choice in conventional growth hormone insufficiency. Selection of children for GHRH treatment may require more careful evaluation and GHRH treatment may have a greater role in children who have less severe growth hormone insufficiency in the presence of suboptimal endogenous growth hormone secretion. The results suggest that a more practical long term approach may be the development of a GHRH depot release preparation which would combine the advantages of several growth hormone pulses per day and the convenience of infrequent administration

We are grateful to Ms PJ Pringle and Mr B Rafferty for undertaking the growth hormone and GHRH assays respectively and to Professor M Thorner and KabiVitrum for supplying us with GHRH 1–40 and GHRH 1–29 We are also grateful to Children Nationwide Medical Research Fund for financial support

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Measuring severity of injuries to children from home accidents

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SUMMARY The severity of injuries from home accidents was assessed in 402 children under the age of 5 treated in the accident department of an inner London hospital. Our child injury severity scale comprises three grades of severity for six types of injury. There was moderate agreement between the observer and an assessor in categorising the cases. Burns and scalds and poisoning caused more severe injuries than other accidents A strong correlation was found between the parent's social class and the severity of the accident, but there was no correlation with ethnic group as indicated by the parents' country of birth. The development of a reliable scale of severity is important if programmes of prevention of accidents to children in the home are to be evaluated successfully.

Accidents are an important cause of mortality and morbidity in children.[1] About one in six children each year in Britain are injured severely enough to attend an accident and emergency department In a population study 44% of children were reported to have had an accident that warranted medical treatment before they were 5 years old; about two thirds of these accidents were in the home, and less than 5% on the roads.[2] More detailed epidemiological studies of accidents to children at home have sought to identify causal factors and suggest ways of prevention.[3–6]

Measures of the severity of injuries are important because plans for prevention might seek to reduce the severity of the injuries, rather than their frequency. Previous studies of accidents to children at home have varied in the composition of subjects and their accidents, as well as in the methods used for measuring the severity of the injuries. Simple[7] or more detailed[8 9] classifications may be made from the medical care given, but the admission of children to hospital depends on social factors as well as on the severity of the injury. The American abbreviated injury scale, designed to assess the severity of injuries to adults in road traffic accidents, has clear grades of injury The abbreviated injury scale seems, however, to have low discriminating power for accidents to children; in one study it classified 89% of children as having a minor injury, 8% as moderate, and remainder severe (including fatal).[5]

We have developed a scale to measure the severity of all accidents to children at home that were treated in the accident department of an inner city hospital. It is based on the scale used by Illingworth in her study of injuries in playgrounds,[11] and has clear definitions and a broad distribution of injuries among categories.

Methods

The measurement of severity was part of a study designed to describe the frequency and types of accidents that happen to children under five in the home in a multiracial population, and to relate these to the home environment [12 13] The study was done in the Central Middlesex hospital, which draws patients from two boroughs in west London. Ethical permission was given by Brent District Health Authority. Details were recorded of all accidents to children under five that happened in the home who were treated in the accident department over a 10 month period in 1983–4.

Because our primary aim was to study accidents in the home, the commonest type of accident in this age group, data were not recorded about other types of accidents. Children given reassurance alone without treatment, children from outside the main catchment area, and 22 children with non-accidental injuries were excluded. A total of 481 children were eligible for the study The records of the accident department were reviewed each week (by RA) and permission to visit the parents was sought by letter.

There were 79 children whose parents refused or who could not be contacted, a response rate of 83%, leaving a sample of 402 parents who were interviewed.

The hospital catchment population for the study covered 21 electoral wards. Data from the 1981 census showed that this was a multiracial and relatively deprived part of London. Three main ethnic groups were defined by the parents' country of birth: British (including the Republic of Ireland), Caribbean, and Asian (predominantly from the Indian subcontinent). The remainder comprised other European and black African parents. Social class was assigned by the Registrar General's classification; this particular population had a proportion of unclassifiable parents because of the high rate of unemployment.

We divided the accidents in the home into six types and classified the injuries retrospectively using information from clinical records of the accident department, the inpatient notes, and the records of the community nurses. The child injury severity scale had definitions for three grades—mild, moderate, and severe (table 1). To test the reliability of the scale, short descriptions of all 402 accidents were written down by the researcher (RA) and scored afterwards by another assessor (MM). The kappa statistic was used to test interobserver agreements.[4]

Results

Classification by the researcher and assessor into the three grades of severity is shown in table 2. Using the scale, the researcher certified that 36% of accidents were mild, 39% moderate, and 24% severe. The kappa statistic (0·58) indicated moderate interobserver agreement. The observers had similar distributions in their disagreements among the categories, suggesting that the differences between them were random rather than systematic.

Accidents were classified as falls, burns and scalds, poisoning, cuts, and 'other'. Almost half (n=195, 48%) of all the accidents, were falls, and most of these were of mild or moderate severity. Table 1, however, shows that some other types of accident—for example, burns and scald (n=49, 12%), and poisoning (n=53, 16%)—stand out as being relatively more severe.

The electoral wards were grouped according to rates of attendance for children in the study compared with their populations of children recorded in the 1981 census. There were five high wards (over 50 attending/1000 children), nine medium (26–50/1000), and seven low (up to 25/1000). There was no correlation between the number of children attend-

Table 1 *Injury severity scale*

Lacerations	
Mild	minor, no treatment minor, suture only
Moderate	requiring further treatment or dressings multiple, with haematoma joint injuries needing immobilisation accompanied by swelling, contusion, or effusion
Severe	requiring admission to hospital
Burns and scalds	
Mild	minor, no further treatment
Moderate	requiring one or two dressings at home
Severe	requiring more than two dressings at home or admission to hospital
Poisoning	
Mild	requiring reassurance only
Moderate	requiring admission to hospital for 24 hours or short term treatment
Severe	requiring admission to hospital for several days
Fractures	
Mild	none included
Moderate	undisplaced, followed up as outpatient accompanied by lacerations
Severe	with deformity or displacement, or both requiring admission to hospital requiring operation under general anaesthetic
Head injuries	
Mild	requiring reassurance only
Moderate	accompanied by another injury (laceration, haematoma, or bruise)
Severe	requiring admission to hospital, accompanied by clinical signs fractured skull with prolonged loss of consciousness
Foreign body (either stuck or swallowed)	
Mild	requiring reassurance only
Moderate	requiring treatment in specialist department requiring admission for observation
Severe	requiring admission for several days

Table 2 *Assessment of severity of injuries by researcher and second assessor*

Second assessment	*Researcher's assessment No (% of total No)*			*Total*
	Mild	*Moderate*	*Severe*	
Mild	106 (26)	28 (7)	5 (1)	139 (35)
Moderate	34 (8)	117 (29)	24 (6)	175 (43)
Severe	6 (2)	13 (3)	69 (17)	88 (22)
Total	146 (36)	158 (39)	98 (24)	402 (100 0)

Table 3 *Type of accident and severity of injury*

Type of accident	*Severity of injury No (%)*			*Total*
	Mild	*Moderate*	*Severe*	
Falls	83 (43)	77 (39)	35 (18)	195
Burns and scalds	6 (12)	14 (29)	29 (59)	49
Poisoning	13 (21)	29 (46)	21 (33)	63
Cuts	23 (43)	21 (39)	10 (18)	54
Others	21 (51)	17 (42)	3 (7)	41
Total	146 (36)	158 (39)	98 (24)	402

$\chi^2=54\ 87$, DF8, $p<0001$

Table 4 *Attendance from each electoral ward and severity of injury*

Attendance rates/1000 children aged 0–4 in the electoral ward	*Severity of injury No (%)*			*Total*
	Mild	*Moderate*	*Severe*	
>50	55 (32)	76 (44)	41 (24)	172
26–50	70 (42)	56 (34)	41 (25)	167
<25	21 (33)	26 (41)	16 (25)	63
Total	146 (36)	158 (39)	98 (24)	402

$\chi^2=5{\cdot}06$, DF4, $p<0\ 28$

Table 5 *Parent's country of birth and severity of injury*

Severity of injury	*Parent's country of birth*			
	British Isles	*Asian*	*Caribbean*	*Others*
Mild	69 (38)	48 (38)	17 (28)	12 (39)
Moderate	64 (35)	56 (44)	24 (39)	14 (45)
Severe	50 (27)	23 (18)	20 (33)	5 (16)
Total	183 (100)	127 (100)	61 (100)	31 (100)

$\chi^2=8\ 64$, DF6, $p<0\ 19$

Table 6 *Parent's social class and severity of injury*

Social class	*Severity of injury*			
	Mild	*Moderate*	*Severe*	*Total*
I and II	16 (44)	16 (44)	4 (11)	36
III non-manual	16 (28)	29 (50)	13 (22)	58
III manual	51 (37)	62 (45)	26 (19)	139
IV	31 (39)	24 (30)	25 (31)	80
V	17 (34)	17 (34)	16 (32)	50
Not known	15 (38)	10 (26)	14 (36)	39
Total	146 (36)	158 (39)	98 (24)	402 (100 0)

$\chi^2=18\ 39$, DF=10, $p<0{\cdot}05$

ing from each ward and the distribution or severity of injuries found (table 4)

There were minor but not significant variations in the severity of injuries among the ethnic groups; children of Caribbean born parents had a slightly larger number of severe accidents when compared with the other groups combined (table 5). In contrast, there was a definite association in the trend of severity of injuries and social class. Children with social class I and II parents had fewer severe injuries; these were more common in those from classes IV and V (table 6).

Discussion

The severity rating scale used in this study of accidents to children in the home was based on information gathered by a doctor from hospital records. The definitions took into account information gleaned at the time of first attendance at the accident department, and also information recorded subsequently. We know of no previous study that has compared agreement between two observers on the severity of injuries of such accidents. In this study the agreement was moderate and showed no systematic differences between the two observers.

We found little difference in severity when we analysed the accidents by ethnic group, but a strong trend towards more severe injuries in lower social classes This finding is in line with other results from our study that show that social class, but not race, is strongly associated with the frequency of accidents.[13] Children from deprived families had more accidents, and these were more serious It is of note that burns and scalds, and poisoning, were much more likely to be severe than the other types of accident. More research is needed to explore other factors affecting the severity of injuries.

The uniformity of proportions when severity was correlated with distance from the hospital was of interest. In this part of London there are several hospitals with catchment areas that overlap, so that access is probably not a major determinant of hospital use Our severity scale for children who received treatment seems to reflect clinical thresholds that are important to patients at all distances in this population.

The number of accidents taken to hospital accident departments is not a complete measure of all accidents. Some, especially in rural areas, are treated by general practitioners, and many are self treated What factors affect the likelihood of a parent taking a child to a hospital for treatment are complex, but include the time they expect to be kept waiting and the acceptability of the service. If the numbers of accidents dropped the service might improve, and parents might be prepared to take their children to hospital for more minor complaints. This 'iceberg' of morbidity prevents a simple conclusion being drawn merely from attendances as an evaluation of prevention. Only by monitoring the severity of injuries can this effect be considered.

The Royal Society for the Prevention of Accidents has defined an accident as 'a consequence of a sequence of random events, always involving causal factors, with chance alone often determining the resultant severity'.[15] By this definintion an effective plan for prevention of accidents to children would show a reduction in the total number of children attending a hospital after accidents, but without a change in the distribution of the severity of injuries. Many people, however, would intuitively regard this as unlikely. Young children are exploring the world and need a graded experience of risks, some accidents will always occur. A plan for the prevention of accidents to children would be as likely to seek to reduce the severity of the injuries as to reduce their frequency.

Our child injury severity scale showed relatively similar numbers of children in the three groups mild, moderate, and severe. This is in contrast to the pyramidal shape found in some other studies, with few severe accidents, more moderate ones, and many mild ones.[6 9] There are two reasons for this finding. Firstly, we selected only children who needed medical treatment for the study. This process excluded the mildest injuries that required no medical treatment. Secondly, the scale was designed to create a range of severity that reflected the range of clinical cases, as Illingworth's was. We could have created a scale that designated only a small group as severe, in the way that the abbreviated injury scale seems to do, but this seemed less useful than one with a larger group designated severe if the eventual use of a scale would be to measure changes in rates of severity; if the severe group is initially small there would be little to change.

Accidents to children show a downward gradient when correlated with social class. Our study has shown that there is also a social class gradient of severity of injuries, but little difference in severity among ethnic groups. It suggests that strategies for prevention of childhood accidents will need to give special attention to the disadvantaged in our society. Plans that affect everyone equally (such as engineering regulations) or that communicate broadly (such as health education through the media) could, paradoxically, keep these inequalities persisting. Our study gives supporting evidence for the continuing need for positive discrimination in material and personal help for disadvantaged families if we are to make a noticeable impact on the number of accidents to children in the home.[16]

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Comparison of five tests used in diagnosis of neonatal bacteraemia

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SUMMARY The neutrophil count, immature:total neutrophil ratio, C reactive protein assay, nitroblue tetrazolium test and an acridine orange leucocyte cytospin test were evaluated for the diagnosis of neonatal bacteraemia. The acridine orange leucocyte cytospin test gave the highest specificity and positive predictive accuracy, but was less sensitive than the neutrophil count, C reactive protein assay or nitroblue tetrazolium test, particularly for the diagnosis of bacteraemia caused by coagulase negative staphylococci. No single test gave the sensitivity, specificity, and positive predictive accuracy of the combined results of the acridine orange leucocyte cytospin, C reactive protein, and nitroblue tetrazolium tests.

Bacteraemia is a common cause of morbidity and mortality among neonates in intensive care units,[1] but the clinical signs are often non-specific.[2] It has been suggested that a combination of haematological and biochemical tests may provide a more rapid and accurate diagnosis of bacteraemia than conventional microbiological methods[3 4] and the use of a 'sepsis screen' may reduce the amount of antibiotics used [5]

We selected five tests including the acridine orange leucocyte cytospin test that could be performed rapidly and economically, and adapted them for use with small amounts of blood. We report an evaluation of these tests in neonates in a regional referral neonatal unit with suspected bacteraemia.

Patients and methods

The regional neonatal unit admits about 500 babies each year with both medical and surgical illnesses from this and other units in West Yorkshire More than 60% of the admissions to the regional neonatal unit are premature neonates with the respiratory distress syndrome. Blood, cerebrospinal fluid, and urine were collected from all neonates with suspected bacteraemia. Clinical signs of bacteraemia included unstable temperature, apnoea, bradycardia, poor peripheral perfusion, or hypotension.

Blood was collected by arterial or venous puncture after skin disinfection with 70% isopropyl alcohol or povidone iodine. Up to 2 ml was divided into three containers as follows: one 0·5 ml sample was anticoagulated with edetic acid (final concentration 1·5–2 mg/l), 0·5 ml was placed in a tube without anticoagulant and 0·5–1 ml was inoculated aseptically into 80 ml of broth (Signal medium BC 102, Oxoid Ltd, Basingstoke). An indicator was inserted through the rubber seal[6] and the broth culture incubated at 37°C on a Denley (prototype) continuous shaker at 160 rpm for 4–18 hours, it was then left in the incubator for up to 10 days. Bottles with signs of bacterial growth and all bottles after 48 hours of incubation were subcultured by inoculation of 0·1 ml aliquots on to heated blood agar and 5% horse blood agar plates, which were incubated at 37°C in 5% carbon dioxide and at 37°C anaerobically, respectively, for up to 48 hours. Isolates from the blood cultures were identified using conventional microbiological techniques.[7] Coagulase negative staphylococci were defined as catalase positive, coagulase negative, deoxyribonuclease negative Gram positive cocci.

The sample containing edetic acid was used for the neutrophil count, immature:total neutrophil ratio, nitroblue tetrazolium test, and the acridine orange leucocyte cytospin test The total nucleated cell count was made on a Coulter counter and a differential cell count from a Giemsa stained blood film gave the immature total neutrophil ratio.[8] An age adjusted normal range[9] was used to assess the neutrophil counts, and neutropenia or neutrophilia were considered abnormal. A normal range of up to 0·2 was used for the immature:total neutrophil ratio.[4]

The nitroblue tetrazolium test was done by a modified cytocentrifuge technique.[10] 50 μl of blood containing edetic acid was added to 100 μl of 0·15M phosphate buffered saline (pH 7·2) containing 0·075% (w/v) nitroblue tetrazolium in polystyrene tubes. The mixture was incubated at 37°C for 20 minutes, and then for a further five minutes at room temperature. Red cells were lysed by the addition of 1·2 ml of hypotonic formal saline (10% formalin containing 0·025M sodium chloride). When red cell lysis was complete (usually after one minute), 2·8 ml of 0·2M sodium chloride was added, and after mixing the tubes were centrifuged at 258 *g* for five minutes. The supernatant was discarded by inversion and 50 μl of 22% (w/v) bovine albumin (Ortho Diagnostics, New Jersey, USA) was added to resuspend the deposit that was then prepared as a cellular monolayer with a Shandon 2 cytospin at 1000 rpm for five minutes. The cytospin preparation was heat fixed at 70°C for two minutes and stained with 0·15% (w/v) aqueous rhodanile blue dye that had been passed through an 0·2 μm cellulose acetate filter to remove any deposit. Stained slides were examined by light microscopy at a magnification of 400. The percentage of 100 neutrophils containing nitroblue tetrazolium formazan gave the nitroblue tetrazolium score, with a normal range of up to 13%.[11] The metabolic integrity of the neutrophils was assessed using phorbol myristic acid.[12]

The acridine orange leukocyte cytospin test was used to detect bacteria in neutrophils from whole blood. The test was performed by adding 50 μl of acridine orange (100 mg/l in 0·15M sodium chloride) to 50 μl of whole blood containing edetic acid in polystyrene tubes. Red cells were lysed and a cellular monolayer prepared as for the nitroblue tetrazolium test. The cytospin slide preparations were heat fixed and then examined by ultraviolet microscopy using a rhodamine filter set at a magnification of 1000. Intracellular bacteria were coloured bright red against a dull red background. The presence of bacteria was confirmed with a duplicate cytospin preparation or by overstaining the acridine orange leucocyte cytospin preparation with Gram's stain.

A latex agglutination method[13] was used to screen serum samples for C reactive protein concentrations of more than 10 mg/l after dilution of serum 1/10 in 0·15M sodium chloride. C reactive protein concentrations of more than 10 mg/l were quantified using an enzyme multiplied immunoassay.[14]

Results

Two hundred samples of blood were collected from 100 neonates including 68 who had been admitted with prematurity and the respiratory distress syndrome. The mean gestational age of the premature neonates was 30·2 weeks (range 24–35) and the mean birth weight was 1410 g (range 700–2470). The remaining 32 babies were admitted with a variety of other surgical and medical diagnoses. One sample of blood only was collected from each of 65 of the neonates; the number of samples taken from the other 35 varied from two to 10.

After making certain that only one sample was considered from each episode of suspected bacteraemia,[5] and that contaminated samples had been excluded,[7] 188 episodes of suspected bacteraemia were considered for further study, of which 34 were associated with positive and 154 with negative blood cultures. The bacterial species isolated during episodes of suspected bacteraemia are shown in table 1. Twenty one (62%) of the 34 blood culture isolates were coagulase negative staphylococci. The proportion of these that were caused by contamination was not known. There were no episodes of bacterial meningitis during the study. There was one urinary tract infection that was associated with *Escherichia coli* septicaemia.

The sensitivity, specificity, and positive predictive accuracy of each test are shown in table 2. The neutrophil count was abnormal in 24 (71%) of the 34 episodes associated with positive blood cultures, but was also abnormal in 65 (42%) of 154 episodes with negative blood cultures. Though the immature:total neutrophil ratio was less often abnormal when the blood culture was negative, only 10 (29%) of 34 episodes associated with positive blood cultures gave an abnormal immature:total neutrophil ratio. Even after exclusion of coagulase negative staphylococci, eight of 13 episodes were associated with immature:total neutrophil ratios of less than 0·12.

The C reactive protein concentration was less than 10 mg/l in 10 (29%) of the 34 episodes associated with positive blood cultures, but in only two (15%) of 13 episodes after the exclusion of

Table 1 *Bacterial species isolated from neonates with episodes of suspected bacteraemia*

Bacterial species	*No of isolates*
Coagulase negative staphylococci	21
Pseudomonas aeruginosa	3
Staphylococcus aureus	3
Enterococcus faecalis	2
Enterococcus faecium	1
Group B streptococcus	1
Listeria monocytogenes	1
Escherichia coli	1
Serratia liquefaciens	1
Total	34

Table 2 *Sensitivity, specificity, and positive predictive accuracy of tests for the diagnosis of bacteraemia*

	Sensitivity (%)	*Sensitivity excluding coagulase negative staphylococci (%)*	*Specificity (%)*	*Positive predictive accuracy (%)*
Neutrophil count	70·6	84·6	57·8	27·0
Immature total neutrophil ratio	29·4	30·8	82·5	27·0
C reactive protein assay	61·8	84·6	81·2	42·0
Nitroblue tetrazolium test	76·5	100·0	70·8	36·6
Acridine orange leucocyte cytospin test	38·2	76·7	94·2	59·1
Two or three of C reactive protein assay, nitroblue tetrazolium, acridine orange leucocyte cytospin test positive	61·8	92·3	90·3	56·8

Sensitivity—positive blood cultures with positive test, specificity—negative blood cultures with negative test, positive predictive accuracy—positive test with positive blood culture

coagulase negative staphylococci. Though the nitroblue tetrazolium test was positive in all 13 episodes, 45 (29%) of 154 episodes with negative blood cultures were also associated with positive nitroblue tetrazolium tests The acridine orange leucocyte cytospin test identified 10 (77%) of 13 episodes of bacteraemia after exclusion of coagulase negative staphylococci and only nine (6%) of 154 episodes associated with negative blood cultures gave positive acridine orange leucocyte cytospin tests. The acridine orange leucocyte cytospin test, however, only detected 13 (38%) of 34 episodes associated with positive blood cultures when coagulase negative staphylococci were included.

The C reactive protein assay, the nitroblue tetrazolium and the acridine orange leucocyte cytospin test gave the highest positive predictive accuracy. Two or three tests were positive in 12 (92%) of the 13 episodes of bacteraemia after exclusion of coagulase negative staphylococci and in 21 (62%) of the 34 episodes associated with positive blood cultures. Coagulase negative staphylococci were isolated from 12 (8%) of the 151 episodes when none or only one of the three tests was positive, and from nine (24%) of the 37 episodes when two or more of the tests were positive. The results of total neutrophil counts and immature:total neutrophil ratios did not improve sensitivity, specificity, or positive predictive accuracy when included in three, four, or five test combinations.

In 15 (10%) of the 154 episodes associated with negative blood cultures two or three of the C reactive protein, nitroblue tetrazolium, and acridine orange leucocyte cytospin tests were positive. These 15 episodes occurred in neonates who had undergone major operations (n=4), had a tracheo-oesophageal fistula and pneumonia (n=1), and had necrotising enterocolitis (n=1); three babies had received antimicrobial drugs within 24 hours of blood sampling. The remaining six episodes were all associated with positive acridine orange leucocyte cytospin tests, but cultures of the urine and cerebrospinal fluid grew no pathogens.

Discussion

The neutrophil count, immature:total neutrophil ratio, C reactive protein assay, nitroblue tetrazolium test, and acridine orange leucocyte cytospin test were evaluated for the diagnosis of bacteraemia in neonates in a regional unit. All these tests could be done within one hour of blood sampling and used a total blood volume of less than one ml.

Many studies have reported the use of total neutrophil count, immature:total neutrophil ratio or C reactive protein assay for the diagnosis of bacteraemia in neonates. The white cell count is of poor predictive value in neonatal bacteraemia, but the total neutrophil count may be high or low in 80% of such babies.[15] Immature:total neutrophil ratios may also be raised in more than 80%.[15–17] The poor sensitivity of the immature:total neutrophil ratio in this study may have been the result of sampling at the wrong time, because this unit admits a large proportion of very low birthweight 'high-risk' neonates, and also because the immature:total neutrophil ratio may be less sensitive after the first week of life.[18] Though a positive blood culture was never associated with a negative nitroblue tetrazolium test, either C reactive protein assays or nitroblue tetrazolium tests were often positive in association with negative blood cultures.

High specificity and sensitivity have been reported for buffy coat smears prepared from capillary blood and stained with acridine orange.[19] We modified the method to use 50 μl of whole blood mixed with edetic acid and were able to identify 10 (77%) of 13 episodes of bacteraemia after the exclusion of coagulase negative staphylococci. Positive acridine orange leucocyte cytospin tests with negative blood cultures may have been false positive results or may have resulted from transient bacteraemia

Infections with coagulase negative staphylococci are rarely associated with neonatal mortality[20] but coagulase negative staphylococci have replaced Gram negative bacterial species as the commonest isolates from neonatal blood cultures after the first 48 hours of life.[21 22] The high incidence of bacteraemia with coagulase negative staphylococci in premature neonates has been attributed to colonisation of plastic intravascular devices by antibiotic resistant, slime producing strains of coagulase negative staphylococci.[23] Bacteraemia with coagulase negative staphylococci may be associated with the clinical features of septicaemia,[24 25] so coagulase negative staphylococci isolates were included in this study even though the proportion of isolates of coagulase negative staphylococci in blood cultures that could be attributable to contamination was not known.

Only three (14%) of 21 isolates of coagulase negative staphylococci in blood cultures were associated with positive acridine orange leucocyte cytospin tests. The minimum concentration of organisms detectable by the acridine orange leucocyte cytospin technique using 50 μl of whole blood was 20 organisms per ml, suggesting lower concentrations for most of the neonates from whose blood cultures coagulase negative staphylococci had been isolated. This may reflect both the low virulence of coagulase negative staphylococci and the proportion of coagulase negative staphylococci contaminants.

The acridine orange leucocyte cytospin test gave the highest specificity and positive predictive accuracy but was less sensitive than neutrophil count, C reactive protein assay, or the nitroblue tetrazolium test, particularly for the diagnosis of bacteraemia caused by coagulase negative staphylococci. No single test gave the sensitivity, specificity, and positive predictive accuracy of the combined results from the acridine orange leucocyte cytospin test, C reactive protein assay and nitroblue tetrazolium test.

Philip[5] reported a reduction in the use of antibiotics after he started using a combination including estimations of the white cell count, the band:neutrophil ratio, the erythrocyte sedimentation rate, the latex C reactive protein assay and serum haptoglobin concentration for the diagnosis of neonatal sepsis. Many neonatal units use unnecessary antibiotics.[26] This study confirms that a combination of tests may improve the accuracy of diagnosis of neonatal bacteraemia.[4] We intend to follow this study with an evaluation of the influence of this combination of tests on neonatal morbidity and mortality, use of other diagnostic tests, and use of antibiotics in this regional neonatal unit.

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Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome in three siblings

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SUMMARY Two brothers and one sister had three variants of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (the 'TTP-HUS' complex). The sister had a chronic fatal variant of thrombotic thrombocytopenic purpura with severe neurological manifestation. One brother had a chronic relapsing disease but the kidneys were not affected, and the other brother had haemolytic uraemic syndrome. This occurrence in one family supports the hypothesis that haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura are acutally two variants of the same disease.

Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome are two closely related syndromes, in which thrombocytopenia, microangiopathic haemolytic anaemia, fever, and renal impairment are common features.[1] Many authors suggest that these two syndromes actually represent a range of illness with the same basic disease process.[2] Fluctuating neurologic signs are more often observed in thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome is a process mainly affecting the kidneys. Haemolytic uraemic syndrome usually affects children younger than 8 years of age, while thrombotic thrombocytopenic purpura is rare in childhood.[1] [2] The cases described below occurred 17 years apart in three siblings, each sibling manifesting a different variant of the 'TTP-HUS' complex.

Case reports

Case 1. A 1 year old girl, daughter of healthy unrelated Arab parents, with seven healthy sisters and two brothers was admitted in December 1967 with diarrhoea, vomiting, and severe anaemia. On admission she was lethargic, pale, and tachycardic. The blood count showed anaemia, thrombocytopenia, and evidence of microangiopathic haemolysis (table). Coombs' test was negative and the serum

Table *Clinical and laboratory data of the three patients*

	Case 1 *Episodes of disease*			*Case 2* *Episodes of disease*
	December 1967	*February 1968*	*July 1968*	*December 1968*
Age (years)	1	1 year 2 months	1 year 7 months	2 months
Presenting symptoms	Vomiting, diarrhoea	Fever, gingival bleeding	Left hemiparesis, left facial palsy	Fever, lethargy
Blood pressure (mm Hg)		100/60	110/60	
Haemoglobin g/l	43	60	60	35
Reticulocytes (%)	21	6·8	15	5·6
Platelets ×10⁹/l	17	65	13	21
Bilirubin ind/total (µmol/l)	25·7/30·3	59·9/63·3	51·3/59·9	
Lactate dehydrogenase U/l				
Urea (mmol/l)		22·5	12·1	8·2
Other		Proteinuria, red cell casts	Proteinuria, red cell casts	
Treatment	Blood transfusions	Prednisone, azathioprine	Prednisone	Blood transfusions

urea concentration was normal. The patient received blood transfusions and her haemoglobin concentration rose to 92 g/l. She was discharged after 16 days with the diagnosis of anaemia and throbocytopenia.

The patient was readmitted five weeks later for fever and gingival bleeding. On physical examination she was pale, jaundiced, and ecchymotic with submucosal bleeding The haemoglobin was 60 g/l with reticulocytosis of 6·8%, and a platelet count of 65×10^9/l Serum urea concentration was 22·5 mmol/l, and bilirubin 63·3 μmol/l. Urinalysis showed +3 proteinuria and a few blood cell casts (table).

The peripheral smear showed fragmented red blood cells with burr cells. The diagnosis of thrombotic thrombocytopenic purpura was considered. Blood transfusion was given and the patient received prednisone 1 mg/kg/day for two weeks without any improvement in her condition. At this stage, despite normal results for immunological laboratory tests (LE cells, Coombs' test, and antinuclear factor were all negative), immunosuppressive treatment with azathioprine 3 mg/kg/day was given for four weeks, again without any improvement in her condition. She was readmitted two weeks later with severe anaemia, thrombocytopenia, jaundice, transient left facial nerve palsy, and left hemiparesis. Her blood pressure was 110/60 mm Hg. The urea concentration was normal but urinalysis showed proteinuria and red cell casts. Treatment with prednisone 40 mg/day was started with transient improvement Ten months after the onset of her disease, the patient developed generalised convulsions with deep coma and died. The postmortem examination disclosed multiple thrombi in small arterioles and capillaries, with multiple infarcts in the brain. Similar changes in small vessels were found in the skin, kidneys, pancreas, gingiva, and the myocardium. The diagnosis of thrombotic thrombocytopenic purpura was confirmed.

Case 2. The brother of case 1 was diagnosed at the age of 2 months as suffering from thrombotic thrombocytopenic purpura after developing microangiopathic haemolytic anaemia, severe thrombocytopenia, fever, and mild neurological signs (table). After two months in hospital he achieved complete clinical and laboratory remission. The patient was admitted twice more, at the age of 4 and 13 years, with relapses of his disease which were mild and self limiting. At the age of 15 he was admitted to the department of surgery with right lower abdominal pain and confusion. His blood pressure was 120/90 mm Hg Acute appendicitis was suspected and he underwent surgery The appendix was normal After the operation the patient was lethargic with mild confusion. He developed fever, a bleeding tendency with a large haematoma at the site of the incision, and severe anaemia. The patient was transferred to the medical department. Relevant laboratory findings included anaemia, thrombocytopenia, reticulocytosis, and evidence of a haemolytic process. His plasma haptoglobin concentration was 0·3 g/l (normal 2·0–3·0 g/l). Peripheral blood smear showed anisocytosis, poikilocytosis schistocytes, and burr cells. Serum urea concentration and urinalysis were normal His prothrombin time was 50%; partial thromboplastin time, fibrinogen, and fibrinogen degradation products were normal. Direct and indirect Coombs' tests were negative. The diagnosis of thrombotic thrombocy-

			Case 3 *Episodes of disease*			
March 1972	*1981*	*1983*	*January 1981*	*June 1981*	*March 1983*	*August 1984*
4	13	15	1 year 6 months	2	3 years 6 months	5
Jaundice	Jaudice, pallor	Abdominal pain, negative laparotomy, confusion	Fever, anorexia, lethargy, confusion	Fever, haematuria	Fever, haematuria	Fever, dark urine
120/70		120/90				100/60
116	105	70	56	86	110	120
		6	10 6	18	4 4	2
86		27	17	48	15	14
22 2/44 5	59 9/66 7	29 0/42 8	46 1/49 6			107 7/114·6
	1090	1000	2350	1100		
9 3	14·8	14·2	17·9	16 1	18 9	12 5
			Haematuria, red cell casts	Red cell casts, proteinuria	Red cell casts, proteinuria	
			Blood transfusion		Prednisone, blood transfusions	Plasma

topenic purpura was made. Considering the benign nature of his disease in the past, no treatment was started; the last (fourth) episode was short and self limiting. The platelet count, the concentration of lactate dehydrogenase, and the peripheral blood morphology returned to normal within a few days, and the patient was discharged well.

Case 3. The 5 year old brother of cases 1 and 2 was hospitalised at the age of 18 months because of lethargy, anorexia, and jaundice nine days after receiving measles vaccination Microangiopathic haemolytic anaemia, severe thrombocytopenia, and microscopic haematuria with mild proteinuria was found (table) The diagnosis of haemolytic uraemic syndrome was suspected and he received a blood transfusion His clinical and laboratory condition improved but his laboratory test results returned to normal only six months later. Three additional episodes of the disease were at ages 2, 3½, and 5 years. The patient was admitted with fever, microangiopathic haemolytic anaemia, thrombocytopenia, macroscopic haematuria, mild azotaemia, and proteinuria of 2·5–3 g/24 hours. Haemolytic uraemic syndrome was diagnosed. Steroids and blood transfusion were given and there was a rapid improvement Between the episodes of the disease the patient was healthy, with normal full blood count, and normal urinalysis.

Discussion

Familial occurrence of haemolytic uraemic syndrome is well known.[3] Less frequent is the occurrence of thrombotic thrombocytopenic purpura in families. There are only five such case reports in the literature.[4–8] Although recently similar pathogenic mechanisms have been suggested for both disorders,[9] there is only one report of the occurrence of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura in the same family.[10] The cases described here represent the chronic fatal variant of thrombotic thrombocytopenic purpura with dramatic neurological manifestation (case 1), a chronic relapsing variant with no renal disease and only neurological manifestation (case 2), and haemolytic uraemic syndrome (case 3).

Enhanced platelet aggregation plays a major part in the pathogenesis of both thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome. It is possible that some families have predisposition for enhanced platelet aggregation, and that some environmental factor triggers the onset or the relapse of the disease. Such predisposition could result from the deficiency of prostacyclin or any other natural inhibitor of platelet aggregation in the plasma.[9]

The three cases described support the hypothesis that haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura are actually two variants of the same disease with the same pathogenesis. Such a hypothesis would explain the fact that some cases may present a 'border line' picture between thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, as was the case in our third patient.

The recent recognition of mild forms of thrombotic thrombocytopenic purpura may result in a change in the diagnostic criteria for the disease. Indeed even in the series of Ridolfi and Bell only 74% of the patients had the classical triad and only 40% had the entire pentad.[1] We suggest that the combination of thrombocytopenia and Coombs' negative microangiopathic haemolytic anaemia in patients with a family history of thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome should seriously raise the suspicion of a mild form of thrombotic thrombocytopenic purpura (or haemolytic uraemic syndrome) even in the absence of neurological or renal disease, or both.

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Sleep patterns of infants in the first year of life

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SUMMARY A prospective study of 132 infants aged from 1 month to 1 year found that infants who were breast fed or breast plus bottle fed were significantly more likely to wake at night throughout the first year. Social class of the family, parity of the mother, and the weight gain of the infant had no consistent effects. This increased waking was not due to mothers of wakeful infants prolonging breast feeding to soothe their infants.

Many parents of young infants yearn for an uninterrupted night's sleep.[1] Many infants sleep through the night by the age of 3 months and almost all by the age of 6 months, but waking may increase again during the second six months of life.[2,3] Night waking has been associated with perinatal factors,[2,4] colic or snoring,[5] and temperament.[6] Wright *et al*[7] and also Elias *et al*[8] reported that breast feeding for more than six months prolonged night time waking, but others reported no difference.[1,9] Other authors have reported that parity, social class, the infant's birth weight, weight gain, and the age of starting non-milk foods did not affect waking at night.[1,2,4–6,7,10,11] In few of these studies, however, were the data analysed in a way that separated and assessed the independent effects of each of these factors.

We have used data from a prospective study of infants in south east Queensland to show the separate and independent effects of social and nutrition factors on the night waking of infants in the first year of life.

Methods

Four maternal and child health clinics were selected in Brisbane and Ipswich in south east Queensland so as to cover a range of social classes. Mothers with infants born in 1984 and attending these clinics were asked if they would participate in a one year study on the growth and feeding of their infants.

Mothers were interviewed at roughly monthly intervals from the time their infants were 1 month old. Mothers were asked about their social and family conditions at the first interview. During the first and subsequent interviews they were asked if their infants had had any health, feeding, or other problems during the previous month, what milk and other foods had been given, and whether they got up to their infants at night. The infants were weighed at each visit. Infants were considered to wake at night if one or both parents got up at night to the infant and then went back to bed. The data were grouped into intervals of three months (1–3, 3–6, 6–9, and 9–12 months). The milk feeds were classified as breast fed only, bottle fed only, breast plus bottle fed, or weaned from the breast. Infants were counted as having 'solids' if at any time during the three months period they were given non-milk foods. The weight for age of the infants and weight gains were calculated as a percentage of the WHO/NCHS[12] standards using a computer programme which used exact ages and weights.

In these analyses mothers were divided into primiparas and multiparas. The occupations of husbands were used as an indicator of social class. In the analyses they have been divided into upper social class, which included managers, professionals, farmers, and technicians; and lower social class, which included skilled, semiskilled, and unskilled workers, and also the unemployed.[13]

The data were analysed by simple tabulation, χ^2 tests, and by a multifactorial non-parametric method that separated the effects of different factors and tested the independent significance of each.[14,15]

Results

There were 132 infants and their mothers included in these analyses and 117 of these were followed up for the full 12 months.

PATTERNS OF WAKING AT NIGHT

At the age of 1 month, 82 (62%) of the infants were waking more than once a night and a further 38 (29%) were waking at night at least once a week (figure). By the age of 6 months, the number of

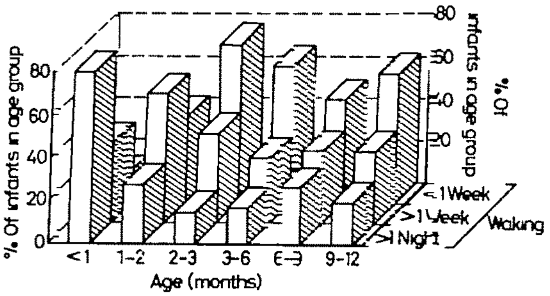

Figure *Percentages of infants waking at night at different ages. The effects of feeding and other factors are not shown but are given in the text. The decline in the percentage of infants who regularly slept through the night is shown in the second half of the first year.*

infants waking more than once a night had dropped to 15 (13%) with a further 31 (27%) waking at least once weekly. The proportion of infants waking at night increased significantly between 6 and 9 months of age (χ^2 test, $p<0·05$).

At 1 and 2 months the median frequency of waking at night was about once a night. After 3 months the median frequency was between once a night and once a week. In the analyses that follow we have divided the infants into those who woke more frequently and those who woke less frequently than the median for age.

FACTORS ASSOCIATED WITH FREQUENT WAKING AT NIGHT

The multifactorial test was used to identify the separate factors associated with waking at night. The factors included in the analyses were the sex of the infant, the type of milk feeding (breast only, bottle only, breast plus bottle, but we excluded those weaned during the period), the giving of 'solid non-milk foods, the percentage of expected weight gain during the previous three months, parity of the mother, and social class of the family. Venn diagrams tabulating these results are available from the authors. The results of these analyses are summarised in the table

The sex of the infant, the parity of the mother, and the social class of the parents showed no significant effects in any of these analyses and therefore have not been included in the table. The type of milk feeding was the only factor that consistently showed significant differences in the first year of life. With one exception, which did not quite reach conventional levels of significance ($p=0·07$), infants receiving breast milk, with or without other milk feeds, woke more at night than those who did not receive breast milk There were occasional significant differences with other factors, but these formed no pattern.

Table *Summary of factors associated with infants waking at night*

Age (months)	*Feeding of infants waking more often than the median value for age (%)*	*p Value*
<1	Breast (67) *v* bottle (29)	<0 01
	Breast+bottle (89) *v* bottle (29)	<0 01
	No infants on solids	
1–3	Breast (49) *v* bottle (29)	NS (0 07)
	Breast+bottle (52) *v* bottle (29)	<0 01
	Solids (35) *v* no solids (57)	0 05
	Weight gain >100% (47) *v* weight gain <100% (47)	NS
3–6	Breast (46) *v* bottle (21)	0 01
	Breast+bottle (56) *v* bottle (21)	<0 01
	All infants had solids	
	Weight gain >100% (26) *v* weight gain <100% (55)	0 04
6–9	Breast (80) *v* bottle (50)	0 02
	Breast+bottle (68) *v* bottle (50)	0 03
	All infants had solids	
	Weight gain >100% (60) *v* weight gain <100% (60)	NS
9–12	No infant exclusively breast fed	
	Breast+bottle (71) *v* bottle (37)	0 02
	All infants had solids	
	Weight gain >100% (48) *v* weight gain <100% (49)	NS

BREAST FEEDING AND WAKING AT NIGHT

We have shown that infants receiving breast milk were more likely to wake at night throughout the first year than those who did not receive breast milk, but this association does not necessarily imply a cause and effect relation. Mothers of wakeful babies may have prolonged breast feeding to help pacify their infants. If this were so, then mothers of wakeful infants should breast feed their infants longer than those whose infants are more settled.

To test this hypothesis we analysed the feeding history of infants who were breast fed at 1 month. Of the 61 infants who received breast milk at 1 month and woke frequently, 57 (90%) were still breast fed at 3 months. Of the 33 'settled' infants who were breast fed at 1 month, 26 (79%) were still breast fed at 3 months. Among the breast fed infants waking frequently at 3 months, 13 (50%) were still breast fed at 6 months compared with 19 (59%) who were waking infrequently at 3 months. None of these differences were significant. These findings do not support the hypothesis that mothers breast feed wakeful infants longer.

Discussion

The group studied in this project was not a statistically random sample of the population but was selected to show how social and other factors might affect infant feeding and health. In a longitudinal study lasting one year there were inevitable drop outs. Most of these were caused by mothers moving to other areas or taking jobs. Each three month period, however, was analysed cross sectionally, so the analyses within each period should be valid.

Most infants wake at night in the first few months, but the proportion decreases until about 6 months of age. From then until 9 months the proportion of infants waking at night in our study increased again and then dropped slightly, but not significantly, from 9 months to 1 year. The lay explanation for this increased wakefulness is 'teething' but this must be regarded as an associated rather than a causal factor.

Using multifactorial methods which separate out the independent effects of each factor, we have found only one factor consistently associated with frequent waking at night, that is breast feeding. Our findings do not support the hypothesis that mothers of wakeful infants prolong breast feeding to soothe those infants back to sleep.[16] There may be a physiological explanation for the increased wakefulness of breast fed infants. Breast milk leaves the stomach more rapidly than formula feeds[17] and this could account for the shorter period of satiety and sleep in breast fed infants. The increased frequency of breast feeding should have biological advantages as frequent stimulation of the breast increases milk supply, but there are concomitant social disadvantages. The total intake of milk is not correlated with the frequency or duration of feeding of the infant.[18]

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Short reports

Radionuclide cystography in vesicoureteric reflux

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SUMMARY We investigated 47 children in whom vesicoureteric reflux was clinically suspected by both conventional radiological and indirect radionuclide cystography. Comparison of the two methods showed no significant difference in their accuracy in detecting vesicoureteric reflux. The advantages and disadvantages of, and indications for, indirect radionuclide cystography are discussed.

The optimal investigation of children with urinary tract infections is controversial and is periodically reviewed.[1] [2] The dilemma, to ensure adequate investigation while avoiding undue trauma or radiation exposure, is familiar to paediatricians and radiologists. The most unpleasant investigation used is undoubtedly the radiological micturating cystogram, which requires urethral catheterisation. This study was performed to determine whether a selected group of children can be spared this cystogram with its associated hazards of infection, radiation exposure and, rarely, urethral stricture formation.

Indirect radionuclide cystography, using an intravenously injected radioactive marker excreted by the kidney, was pioneered by Dodge in 1963.[3] The availability of radiopharmaceuticals more suitable than the original ^{131}I hippuran, in particular ^{99m}Tc DTPA (diethylene triamine penta-acetic acid), and improved imaging with the gamma camera, has now made the technique suitable for routine clinical use.

Patients and methods

Forty seven children aged between 5 and 15 years were studied. All had had urinary tract infections and needed a radiological micturating cystogram because of renal scarring or ureteric dilatation on intravenous urography, recurrent infections or they were being followed up for medically managed vesicoureteric reflux. Informed parental consent was obtained for each child to have an indirect radionuclide cystography performed in addition to a micturating cystogram. The study was approved by the ethical committee of Guy's Hospital and Medical School.

The procedure for indirect radionuclide cystography was explained to the child, who emptied his or her bladder and was then given ^{99m}Tc DTPA intravenously in a dose of 9 mci/m^2 body surface area. Divided renal function measurements were made at this stage. The child was then encouraged to drink freely (a variety of palatable drinks was made available) until he or she felt able to void, usually after about one hour. Boys were positioned standing in front of the gamma camera with a bottle; girls used a specially adapted, well screened commode. When preliminary screening confirmed activity in the bladder rather than the kidneys, the areas over the kidneys, ureters, and bladder were screened for one minue before, during, and 1½ minutes after voiding

Vesicoureteric reflux was diagnosed radiologically if contrast was seen to enter the ureter, and was classified as severe if the pelvicalyceal system was outlined and distended, or if intrarenal reflux was observed. Reflux was diagnosed on indirect radionuclide cystography only if tracer was observed in the pelvis, and was described as severe if it was gross, unequivocal, and immediately obvious on inspecting the images. The results were analysed statistically using McNemar's test.

Results

Three studies using indirect radionuclide cystography were unsuccessful: two children were unable to cooperate and the other failed for technical reasons The table shows the results for the remaining 44 children, expressed in terms of potentially refluxing kidney-ureter 'units.' Two children had only one kidney each and in one child results of both investigations were equivocal for one kidney, so results from 85 units are available for analysis. The two methods were concordant for the detection

Table *Results of indirect radionuclide cystography and radiological micturating cystography in 85 potentially refluxing units*

	All grades of reflux *No (%)*	*Severe reflux only* *No (%)*
Reflux shown by:		
Both studies	30 (35)	21 (25)
Indirect radionuclide cystography only	17 (20)	9 (11)
Radiological micturating cystography only	16 (19)	1 (1)
Neither study	22 (26)	54 (63)
Overall agreement	52 (61)	75 (88)

of reflux in 61% of units, and in 88% for the detection or exclusion of severe reflux (table). There was no significant difference between the methods for detecting reflux if all grades were considered together, but the study using indirect radionuclide cystography detected severe reflux more reliably than the micturating cystogram ($p<0{\cdot}05$)

Discussion

Our results confirm the findings of Hedman *et al*[4] and Merrick *et al*[5] that there is good overall agreement between micturating cystography and radionuclide cystography in the detection of vesicoureteric reflux. In our study there was very good agreement when minor degrees of reflux, of doubtful clinical importance, were excluded. All three studies have shown that reflux may be shown by indirect radionuclide cystography in some patients in whom it was not detected by radiological micturating cystography; some of these cases could be false positives caused by retrograde ureteric peristalsis but an alternative and more likely explanation is that reflux, even when severe, can be an intermittent phenomenon

In children over 5 years of age we had few difficulties in getting cooperation with voiding for the radionuclide cystography. This is considerably less traumatic than conventional micturating cystography in that the risks of bladder catheterisation are avoided, and radiation exposure is reduced to 10% or less of that entailed in conventional micturating cystography. The success of indirect radionuclide cystography, however, depends on patient cooperation and we have not found it suitable for routine use in children under 5 years; it is practicable in selected 3 and 4 year olds Another disadvantage of indirect radionuclide cystography compared with micturating cystography is that the penile urethra is not visualised.

In conclusion, we recommend the use of indirect radionuclide cystography in the following groups of children needing investigation for suspected vesicoureteric reflux: (a) all girls over 5 years of age; (b) girls aged 3–5 years thought likely to be able to cooperate; and (c) boys over 5 years who have already had micturating cystography, thus excluding posterior urethral valves, and who need a repeat investigation during follow up of medically managed vesicoureteric reflux.

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Feasibility of screening all neonates for hearing loss

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SUMMARY We investigated the feasibility and cost of screening all neonates for hearing loss using the auditory response cradle (ARC). At least three full time staff are needed to screen 95% of the 3000 infants delivered each year including those in intensive care. Estimated costs per case detected are between £3000 and £6000 but true costs may be higher.

The screening of all neonates for congenital sensorineural hearing loss is an attractive proposition, because this is the only time before school entry when one has a 'captive population'. Furthermore, early diagnosis and intervention may improve the prognosis for speech and language development.[1]

The auditory response cradle (ARC) (Interface (Research) Ltd) is a screening device which analyses the neonate's behavioural responses to a standardised sound stimulus.[2] The purpose of the present study was to determine the resources needed to screen *all* neonates born in hospital.

Methods

The project was carried out, by one full time screener (JG), over a 12 month period in a teaching hospital with 3000 births each year. An ARC Mk 6 was used and established procedures were followed.[3 4] Babies were not tested on the first day of life.

Every mother was given a leaflet about the test. If the test could not be performed before discharge nursing staff offered the mother an appointment. The screener recorded all births, details of tests performed, and in the case of babies not tested, the reason.

Subsequently, a half time screener was appointed for the regional neonatal intensive care unit (NICU). Data on babies in the NICU were collected over a five month period.

The following assumptions were made in calculating costs: (*a*) that the cost of the ARC was £4400 depreciated over five years. (*b*) that the screener's salary was £6000 a year; and (*c*) that there were no charges for test room, printing, stationery, postage or telephone We also assumed that a consultant audiological service was available for definitive diagnosis and management; that the incidence of congenital sensorineural hearing loss is 1/1000 (1/100 in babies on a NICU); that the ARC detects all cases; and that none would otherwise be detected in the neonatal period.

Results

During the main study period, 2821 full term babies were available for testing and 1293 were screened. In 109 cases the first test was abandoned, usually because the child was restless. Twenty seven babies required a second test having failed a complete first test The total number of tests was 1429. Eight babies were referred for audiological assessment and two had a unilateral hearing loss. No case of bilateral sensorineural hearing loss was found by screening. One mother whose first child had a familial hearing loss was referred directly to the audiologist who confirmed a bilateral sensorineural hearing loss.

The reasons why the remaining 1528 babies were not tested are summarised in the table. An important constraint was the fluctuation in the number of babies who required testing each day (figure). The mean number of tests performed each day was 6·8 (range 4–11). The average screening capacity of one tester was exceeded by the number of births on 99 out of 184 days Appointments for ARC testing after discharge were offered to 122 mothers but only half attended.

In the study on babies in the NICU, 134 babies were admitted of whom 15 died; this left 119 available for study. Seventy one were tested. Four-

Table *Reason why babies were not tested (n=1528)*

Reason	*No of babies*
Insufficient time	426
Discharged at weekend	244
Admitted and discharged at weekend	243
Screener took annual leave	169
Early discharge	131
Cradle faulty	114
Statutory holiday	69
Mother failed to keep appointment	61
Mother refused	40
Screener on sick leave	21
Miscellaneous	10

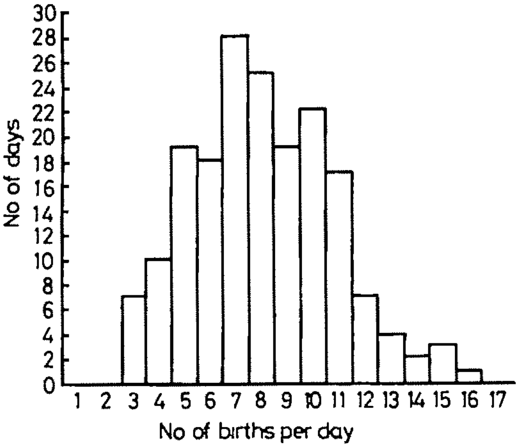

Figure *Distribution of the number of births each day over a six month period*

teen needed a repeat test, three were referred, and one had bilateral sensorineural hearing loss. The 48 not tested were either transferred to referring hospitals or still required intensive care at the conclusion of the study.

Discussion

The two most important constraints on neonatal screening were the fluctuations in the number of births each day and our hospital's early discharge policy. Forty per cent of babies are now discharged before 48 hours of age and an increasing number on the first day.

Although the average time per test was only 30 minutes, testing was often delayed because the baby was crying, restless, or being fed, changed, or examined. It is more realistic to measure the efficiency of an ARC programme in terms of babies tested per week; one full time screener can test between 30 and 40 babies a week.

We thought it would be easier to organise ARC tests in the NICU because babies are often in the unit for long periods, but as soon as the respiratory state was stable the baby, though still too small for an ARC test, was likely to be transferred to the referring hospital.

We estimated the staff needed to screen 95% of babies. Two screeners would be essential on any day when more than eight babies required testing, and one would have to work over bank holidays and weekends. Because of the need for a flexible rota, holiday cover, and time off in lieu for weekend working, three people would be required working at least two and a half full time equivalents. An additional half time equivalent would be needed to include babies in the NICU. Two screeners can share one ARC, but two machines make for greater efficiency.

The cost of detecting one case of bilateral sensorineural hearing loss in full term infants exceeds £5000. The overall cost per case falls to between £3000 and £4000 if babies in the NICU are included and falls further if babies with unilateral sensorineural hearing loss are counted as cases, but unilateral hearing loss does not cause language delay or require treatment so detection in the neonate is of questionable importance.

Generous assumptions were made in calculating these figures. In reality the reliability, sensitivity, and specificity of the ARC are not established[5]; false negatives do occur; and some cases are found by other means, as in our study. The true cost per case is therefore higher.

Neonatal hearing screening of *all* babies born in hospital is expensive and presents serious logistic difficulties, which would apply equally to other screening techniques such as brain stem evoked response audiometry or cochlear emission.[6] The ideal method would be one which the health visitor could use at home, but no such method is currently available. Whether the value of detecting sensorineural hearing loss in the neonate justifies the costs of a screening programme, and whether such a programme can ever replace the seven month screening test are matters for further debate.

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Campylobacter pylori gastritis

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SUMMARY *Campylobacter pylori* colonisation of the stomach is strongly associated with type B non-autoimmune gastritis in adults. In a retrospective study of 38 gastric biopsy specimens taken during upper gastrointestinal endoscopy in children attending this hospital we found *C pylori* in nine (24%). Ten biopsy specimens showed histological evidence of gastritis and *C pylori* was found in eight.

In 1983 Warren and Marshall described the presence of numerous S-shaped spiral bacteria on the antral epithelium of patients with chronic gastritis, and they successfully cultured the organism now called *Campylobacter pylori.*[1] Several reports since then have confirmed that gastric colonisation by *C pylori* is strongly associated with non-autoimmune type B gastritis and peptic ulcer in adults.[2] The histological recognition of *C pylori* by its characteristic curved shape in gastric biopsy specimens correlates well with bacteriological and serological diagnosis,[3] and allows retrospective diagnosis of *C pylori* colonisation.

We performed a retrospective study to determine the prevalance of *C pylori* in gastric biopsy specimens from children endoscoped for upper gastrointestinal symptoms, and we related the presence of clinical features to gastric histology.

Patients and methods

Between January 1981 and February 1987, 111 upper gastrointestinal endoscopies were performed. Suitable biopsy material was available from 38 (34%) patients. The age range of these patients was 1–16 (median 11 years), and there were 20 boys and 18 girls.

The patients' notes were reviewed for details of presentation and follow up. The histological slides were reviewed for presence and character of gastric inflammation and were stained for *C pylori* using a modified Giemsa stain (figure).[4]

Results

C pylori colonisation was detected on histological examination in nine of the 38 cases (24%), six of whom were boys. All patients were 10 years old or over. All 21 patients with histologically normal gastric mucosa were negative for *C pylori.* Ten patients showed histological evidence of chronic gastritis; eight were positive for *C pylori.* In those there was a typical diffuse chronic inflammatory cell infiltration of the lamina propria, two of these showed neutrophils within the glandular epithelium ('active' chronic gastritis) and in four there were mucosal lymphoid follicles. The histology of the two cases negative for *C pylori* but who had gastritis was different: one showed 'lymphocytic gastritis' and the other showed bile reflux gastritis. In seven patients the histology was normal apart from small focal aggregates of lymphocytes, often around a gland; only one of these showed *C pylori* colonisation. The clinical features of the study population are shown in the table. Duration of symptoms before endoscopy ranged from two months to 10 years (median 12 months). Epigastric pain was a distinctive feature of the patients who were positive for *C pylori.* It was present in seven of the nine patients; the presentation in the other two patients was anaemia in one

Figure *Antral mucosa from a case of antral gastritis showing colonisation by C pylori (modified Giemsa stain, original magnification × 300).*

Table *Clinical features of study population*

	Children positive for C pylori	*Children negative for C pylori*
Epigastric pain	7	3
Periumbilical pain	—	13
Vomiting	5	6
Anaemia	1	1
Gastrooesophageal reflux	—	5
Dysphagia	—	1
Duodenal ulcer	2	—
Family history of peptic ulcer	3	—

The duration of symptoms before endoscopy ranged from two months to 10 years (median 12 months)

and vomiting in the other. Three patients with no *C pylori* but who had epigastric pain had diagnoses of bile reflux gastritis, lymphocytic gastritis, and diverticulum of the duodenum, respectively. In contrast, periumbilical pain typical of recurrent abdominal pain of childhood was found only in the patients who were negative for *C pylori*. Vomiting often accompanied epigastric pain in the group who were positive for *C pylori*, but it was also found in the group without *C pylori*. Two patients had radiologically and endoscopically proved duodenal ulcer, and three patients (including the two with duodenal ulcer) had a family history of duodenal ulcer. Follow up information was available in seven of the nine patients who were positive for *C pylori* in a period ranging from one to seven years after biopsy. Four of these patients have remained symptomatic including the two with duodenal ulcer who have been treated with H_2 receptor blockers. Two became asymptomatic, and the seventh patient later developed a medullablastoma that has overshadowed her abdominal symptoms.

Discussion

Recurrent abdominal pain is common in childhood and the studies of the late John Apley show that an organic cause is found in only a few cases[5] Chronic non-specific abdominal pain of childhood is typically central and periumbilical in location.[5] Epigastric pain is less common and usually leads to investigation for an organic cause. *C pylori* associated antral gastritis should be considered in those patients with epigastric symptoms. The diagnosis requires an antral biopsy specimen to be taken for histology or microbiology, or both, as the endoscopy appearance may be normal, although a micronodular appearance of the antrum is characteristic if found. Duodenal ulcer will be found in association with antral gastritis in a proportion of cases.

The role of *C pylori* in gastritis and the progression to peptic ulcer remains to be established. *C pylori* colonisation of the antrum is associated with active gastritis and active gastritis is associated with duodenal ulceration.[6] The emergence of *C pylori* represents another identifiable cause for recurrent abdominal pain in childhood and studies including follow up in childhood may help to elucidate the natural history of peptic ulcer disease.

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656 *Archives of Disease in Childhood,* 1988, 63

Early sodium intake and later blood pressure in preterm infants

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SUMMARY The relation between early salt intake and later hypertension is debated. As part of a larger feeding study, 347 preterm infants were randomly assigned to receive early diets differing grossly in sodium content. Feeding a high sodium preterm formula in the neonatal period did not influence arterial blood pressure at 18 months (corrected) age.

Whether the level of salt intake in early life influences later blood pressure is uncertain, yet numerous authorities recommend avoidance of high sodium intake in infancy.[1-4] Most information in this area is epidemiological and inconclusive. Controlled, prospective data are scanty and conflicting.[2-3] In this study we recorded blood pressure at 18 months post-term in 347 preterm infants who had been assigned randomly, for their early postpartum weeks, to diets differing significantly in sodium content.

Subjects and methods

In a larger five centre study,[5] infants were assigned randomly to the following diets: in centres 1–3, banked donor breast milk *v* a preterm formula ('Osterprem,' Farley Health Products Ltd) as sole diets (trial 1) or as supplements to expressed maternal breast milk (trial 2); and in centres 4 and 5, standard 'term' formula ('Osterfeed,' Farley Health Products Ltd) *v* the preterm formula as sole diets (trial 3) or supplements to expressed maternal breast milk (trial 4). In trials 2 and 4, mothers provided a median of 46% of their infants' feed volume as expressed maternal breast milk. Mean (SE) sodium contents of the diets were: banked milk, 7·2 (0·1) mmol/l (averaged over hospital stay); standard formula, 8·3 mmol/l; and preterm formula, 19·6 mmol/l. The variable contribution to sodium intake from expressed maternal breast milk for infants in trials 2 and 4 was measured in 1776, 24 hour milk collections (overall mean (SE) sodium content, 11·0 (0·15) mmol/l). Additional sodium received enterally was recorded daily. There was no difference between feed groups in sodium intake administered intravenously to sick infants before attaining full enteral feeds.

Infants remained on the assigned diets until they reached 2000 g or were discharged. Postdischarge feeding regimes (standard formula or breast feeding) did not differ between randomised feed groups. At 18 months of age, corrected for prematurity, systolic and diastolic blood pressures were recorded with a conventional sphygonomanometer by a cuff with integrated bladder and size appropriate to the infant's weight and age.

Results

As there was no difference in blood pressure between infants fed donor breast milk or standard formula, data were combined to compare randomly infants fed 'low sodium' donor milk or standard formula *v* 'high sodium' preterm formula, as sole diets (study 1; trials 1 and 3 above, combined) or in conjunction with expressed maternal breast milk (study 2; trials 2 plus 4).

In study 1, the low sodium group achieved, on full feeds, a mean (SE) sodium intake of 1·8 (0·06) mmol/kg/day compared with 3·6 (0·07) mmol/kg/day in the high sodium group ($p<0·0001$, see table). In study 2, corresponding intakes were 1·8 (0·08) and 2·8 (0·07) mmol/kg/day ($p<0·0001$). Infants on the preterm formula took longer to attain full enteral feeds, but spent less time in hospital and therefore on the assigned diet (see table).

No group differences were found in systolic or diastolic blood pressure at 18 months in either study (see table). This was confirmed in a subgroup of 87 infants under 1200 g birth weight, despite the longer period (mean 60 days) on the diet allocated.

A small trend to higher blood pressure in boys than in girls—systolic; 97·9 (0·7) *v* 96·2 (0·7) mm Hg and diastolic 66·4 (0·6) *v* 64·9 (0·6) mm Hg—was not significant.

Discussion

Sodium content in available preterm infant formulas varies greatly, though in most products it is substantially higher than in standard formulas or breast milk. While these special feeds have been designed

Table *Effect of early diet on blood pressure at 18 months (corrected) age in two randomised studies Also shown are the sodium intakes on full enteral feeds and details of the study population in each feed group*

	*Study 1**		*Study 2†*	
	Banked breast milk/term formula (n=56)	*'High sodium' preterm formula (n=54)*	*Banked breast milk/term formula + expressed maternal breast milk (n=116)*	*'High sodium' preterm formula + expressed maternal breast milk (n=121)*
Mean (SE) sodium intake mmol/kg/day	1·8 (0·06)	3·6 (0·04)	1·8 (0·08)	2·8 (0·07)
Mean (SE) gestation (weeks)	31 (0·4)	31 (0·3)	31 (0·3)	31 (0·2)
Mean (SE) birth weight (g)	1373 (40)	1408 (36)	1400 (28)	1405 (25)
Sex M:F	26/30	24/30	61/55	67/54
Median days (quartiles)				
To full enteral feeds	7 (6, 11)	9 (7, 13)	7 (5, 10)	8 (6, 10)
On assigned diet	37 (22, 50)	27 (18, 38)	30 (21, 50)	27 (18, 39)
Mean (SE) blood pressure at 18 months (mm Hg)				
Systolic	97·1 (1·3)	96·6 (1·3)	97·8 (0·9)	96·6 (0·9)
Diastolic	65·4 (1·1)	66·1 (0·8)	65·8 (0·7)	65·5 (0·7)

*Study 1 compares 'low sodium' diets (banked breast milk or standard 'term' formula) with a 'high sodium' preterm formula †Study 2 compares banked breast milk or standard term formula with 'high sodium' preterm formula as supplements to expressed maternal breast milk

to meet high sodium requirements of preterm neonates, this requirement falls postnatally. Thus sodium provided in preterm formulas represents a compromise, and many babies may receive unnecessarily high intakes during their later weeks in hospital. Our analysis was prompted by the increasing use of preterm formulas and concern that high intakes of salt may 'imprint' or 'programme' future blood pressure. Furthermore, we considered that preterm infants might prove more sensitive than term infants to early dietary 'programming'.

We found, however, no effect of early diet on blood pressure at 18 months (corrected) age. The intakes of sodium compared were less extreme than in the randomised study on full term infants of Whitten and Stewart, who also found no effect of early salt on later blood pressure,[2] though the intake in those fed exclusively on preterm formula in our study was higher than recommended for early infancy.[4] The diets we used differed in other respects than their sodium content[5]; these differences would have enhanced further the difference in renal solute loading. While we recognise that 18 months post-term is still early to examine a dietary effect on blood pressure, 'tracking' for blood pressure has been observed in the first postnatal year.[6]

In the short term we have not seen an increase in clinical oedema or hypernatraemia in infants fed on a preterm formula providing 3·6 mmol of sodium per kg each day (unpublished data). In this study our follow up data, obtained thus far only to 18 months, do not support the view that high sodium preterm formulas cause a later rise of blood pressure, or the more general thesis that a high salt intake in early infancy has an adverse imprinting effect on arterial pressure. Nevertheless, our continued follow up of this cohort into adulthood will be important in the further exploration of this area.

We thank the staff of the special care baby units in Cambridge, Ipswich, King's Lynn, Norwich, and Sheffield for their help and cooperation, and Farley Health Products Ltd for financial support

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658 *Archives of Disease in Childhood,* 1988, 63

Silastic catheters for antibiotics in cystic fibrosis

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SUMMARY A randomised comparison of percutaneous Silastic catheters and conventional intravenous cannulae for giving intravenous antibiotics in patients with cystic fibrosis showed that Silastic catheters were favoured by the patient, lasted longer, and had fewer complications.

Repeated courses of intravenous antibiotics in patients with cystic fibrosis have led to an improved prognosis,[1] but they can cause frequent problems with venous access.

Our practice in the management of lung infection in cystic fibrosis is to give intravenous antibiotics early as soon as there is evidence of deterioration—as suggested by an increase in symptoms or signs, deterioration in lung function or x ray pictures, poor weight gain, or growth failure—rather than on a regular basis. Although the frequency of intravenous courses tends to increase after colonisation with *Pseudomonas aeruginosa,* the need is very variable with some patients requiring only one course a year or less. This makes the use of permanent indwelling lines for treatment in cystic fibrosis inappropriate in most cases.

The aim of this study was to compare a 'short' Silastic catheter with a conventional intravenous cannula for giving intravenous antibiotics in patients with cystic fibrosis.

Patients and methods

Twenty children with cystic fibrosis with a median age of 13 years (range 5 to 16 years) admitted for intravenous antibiotics between October 1986 and March 1987 participated in the study. This was the first admission for six patients and no patient had received a previous course of treatment through a Silastic catheter. They were allocated by random numbers to receive antibiotics by either a Silastic catheter or a conventional intravenous cannula; there were 10 patients in each group.

The catheter or cannula was inserted by one of three doctors experienced in the techniques. Fifteen centimetres of Silastic catheter (internal diameter 0·3 mm; Dow Corning) was inserted into the brachial vein by a 19 gauge butterfly needle (Abbott), so that the tip was in a large calibre vein. The butterfly needle was then removed and the line connected to a 25 gauge butterfly needle. This method is almost identical to that described by Shaw[2] and is commonly used for neonatal parenteral feeding.[3] Practical hints for inserting a line are summarised in table 1. Intravenous cannulae (Venflon: size 20 or 22 guage) were inserted into a vein in the hand or forearm in the conventional manner. No local anaesthetic was used for any patient.

Intravenous heparinised saline (1 µ/ml) was given continuously at 1 ml per hour by a portable battery operated pump (Grazeby Medical). Intravenous antibiotics: tobramycin, either alone or together with azlocillin, ceftazidime, or cefuroxime, were given at the manufacturers recommended dilution by slow bolus over 10 minutes and the course continued until clinical improvement had occurred and lung function improved.

After insertion all lines were left undisturbed except in the event of possible complications when the line was inspected under aseptic conditions and the problem resolved or the line replaced.

The patient's opinion of the mode of venous access was sought using a visual analogue scale (0=awful; 10=excellent). Patients were allowed to continue intravenous treatment at home if conditions were felt to be suitable. Parental consent was obtained for all patients.

Results were analysed using the Wilcoxon Rank Sum test.

Table 1 *Practical hints*

When inserting a line:

(1) Always blunt the tip of the 25 gauge butterfly needle before threading it into the Silastic catheter to reduce the risk of puncturing the line
(2) Aim to thread the whole length of the needle into the catheter to prevent the line 'blowing' apart when in use
(3) Always remember to thread the plastic needle guard over the catheter before inserting the needle to help to prevent leakage
(4) Use 'Luer lock' syringes in the pump

Faulty lines:

(1) The commonest problems occur at the butterfly/catheter connection
(2) When flushing a line examine this connection while flushing. Leaks may otherwise be missed.
(3) Beware blockage in the butterfly needle Always try changing the butterfly before giving up!

Table 2 *Comparison of the Silastic catheter and cannula for the administration of antibiotics in children with cystic fibrosis. Results are mean (SD)*

	Silastic catheter (n=10)	*Cannula (n=19)*	*p Value*
Line life (days)	8·4 (4·5)	4·0 (2·1)	0·001
Lines/patient	1·8 (0·42)	2·9 (1·1)	<0·05
Length of intravenous course (days)	15·2 (4·6)	11·7 (1·9)	NS
Patient opinion	8·8 (1·7)	5·7 (2·4)	<0·01
Patient opinion (excluding first admissions)	9·4 (1·0)	6·1 (2·5)	0·01

Results

Line life for Silastic catheters was twice that of cannulae and the number of venepunctures required for venous access was halved. For this latter reason patient opinion was strongly in favour of Silastic catheters. Patients also found that much less or no pain was experienced when antibiotics were given through a Silastic catheter. The results are summarised in table 2.

Cannulae were associated with more complications, but none was serious. The most common problem for Silastic catheters was occlusion of the line (seven episodes) and for intravenous cannulae it was fluid leaking into the tissues (21 episodes). Thrombophlebitis occurred more commonly with intravenous cannulae (three episodes) than for Silastic catheters (one episode). The incidence was not related to the antibiotic combination used. There were no episodes of major sepsis.

Domiciliary treatment was possible in only four patients (three with Silastic catheters, one with a cannula) for a mean period of 6·75 days. All other patients were considered unsuitable for a variety of reasons including other medical or social problems, poor treatment compliance, first hospital admission, or preference to stay in hospital.

Discussion

These results confirm that the use of 'short' Silastic catheters improve quality of life for this group of patients, allowing them to continue a more normal and mobile pattern of life than previously. Some patients have continued to attend school and work during treatment.

Since this study, Silastic catheters have been used electively for over 40 courses of intravenous antibiotics. Most have required only one line for the whole course of treatment. Mean line life has increased considerably to 12·4 days and more than half the patients have been able to continue intravenous treatment at home.

Undoubtedly more experience in the care of these lines has increased their value. Domiciliary treatment has been made more easily available for patients because of the reduction in number of lines required for each course of antibiotics. Many of our patients travel over 50 miles to hospital and returning to hospital for a new line would be extremely inconvenient. It should also be remembered that domiciliary treatment relieves pressure on hospital beds allowing their more efficient use.

We would like to thank the nursing staff at the Children's Hospital for their help during this study

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660 *Archives of Disease in Childhood,* 1988, 63

Free amino acid content of the vitreous humour in cot deaths

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SUMMARY The concentration of 27 amino acids in the vitreous humour was analysed in 120 cot deaths. Baseline data for age and postmortem interval are presented and the concentrations compared with the normal reference range for plasma. The results do not indicate that a specific aminoacidopathy is a factor in cot deaths

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Since 1979 cot deaths have been investigated as part of an overall survey of post-perinatal infant mortality in Glasgow and latterly (1981–2) in a national study for the whole of Scotland. In an attempt to exclude a specific aminoacidopathy as a cause of cot death the free amino acid content of the vitreous humour was analysed in a number of the Glasgow cases. To our knowledge this has not been previously documented, although there are two reports of vitreous amino acid studies in adults.[2 3]

Methods

Vitreous humour was aspirated before postmortem examination at the lateral angle of the eye from infants in an unselected series of 120 cot deaths in the Glasgow area (1979–84) representing 54% of the total number of cases in that period The series included 72 boys and 48 girls and reflected the 3:2 male preponderance of cot deaths in our area and in other series.[4]

The cases were all infants under 1 year of age who had died suddenly and unexpectedly at home without a preceding illness or significant symptoms and as such all did not fit the standard definition of sudden infant death syndrome (SIDS).[5]

The postmortem examinations were carried out in accordance with the instructions of the Procurator Fiscal and followed a standard protocol which included histology of the major organs and selective microbiology A specific cause of death was established in 13 cases (11%) and nine had other incidental conditions.

One ml of vitreous humour was deproteinised by adding 50 mg of salicylsulphonic acid and mixing the resultant solution. After centrifugation at 2000 g for 10 minutes the protein free supernatant was stored at −25°C before analysis 100 μl samples were applied to both columns of a Technicon TSM aminoacid analyser with norleucine being used as an internal standard Peak heights and widths were fed into a Wang 2200 computer for production of printed results expressed in μmol/l.

The results for 27 individual amino acids were analysed by normal distribution statistics, linear regression analysis, and the Mann–Whitney rank sum test for samples of unequal size by means of a

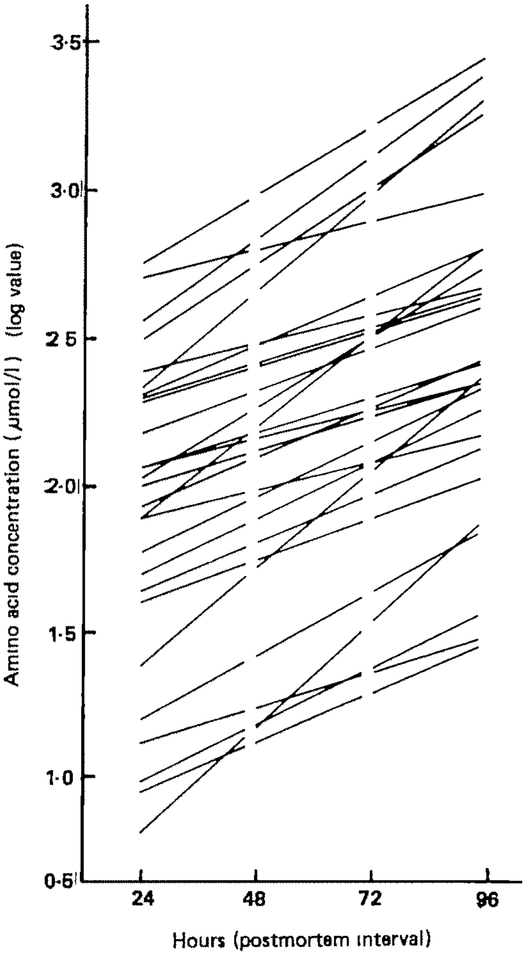

Fig 1 *Logarithmic linear regression analysis of amino acid concentrations by postmortem interval*

computer programme kindly made available by the department of surgery, Glasgow Royal Infirmary.

The cases were arbitrarily divided into those sampled 1–12 hours (n=32), 13–24 hours (n=26), 25–48 hours (n=35), and 49–>96 hours (n=27) after the infant was last seen alive (postmortem interval), and by chronological age groups of 1–4 weeks (n=7), 5–13 weeks (n=45), 14–26 weeks (n=37), and 27–52 weeks (n=31)

Results

Logarithmic linear regression analysis showed that amino acid concentrations were directly related to the postmortem interval (fig 1), and, except for α-aminobutyric acid and valine, inversely related to the chronological age of the infant.

The increase in concentration with time after death was significant ($p<0.01$) for six amino acids in the 13–24 hour postmortem interval group, 13 amino acids in the 25–48 hour group, and 23 amino acids in the 49–>96 hour group. In the combined over 24 hour groups (n=62) the increase was significant ($p<0.002$) for all 27 of the amino acids compared with those sampled less than 24 hours after death (n=58).

The decrease in concentration with chronological age was significant ($p<0.01$) for only nine amino acids in the 27–52 weeks age group. Numbers in the 1–4 weeks neonatal age group (n=7) were too small for adequate comparison.

The mean concentration of 25 amino acids was higher in girls but the difference did not attain significance at the 0·01 level. In one amino acid (γ-aminobutyric acid) the concentration was significantly higher ($p<0.002$) in boys than girls.

Altogether 2433 (82%) of all the (2945) results were within the normal age related plasma reference range (3SD) for this hospital with 86% in the normal range in the combined under 24 hour postmortem interval group and 79% in the normal range in the over 24 hour group (fig 2). Hydroxyproline concentrations were unrecordable in 64% of cases in the under 24 hour group. Ethanolamine and γ-aminobutyric acid were excluded as age related plasma concentrations were not available.

Three cases had abnormal vitreous phenylalanine:tyrosine ratios and were probably examples of transient phenylalaninaemia occurring in early infancy, although in one case the ratio was particularly high (36:1). In a fourth case there was a decrease in the phenylalanine:tyrosine ratio (1:2·8) entirely due to an increase in tyrosine concentration perhaps related to infantile tyrosinaemia.

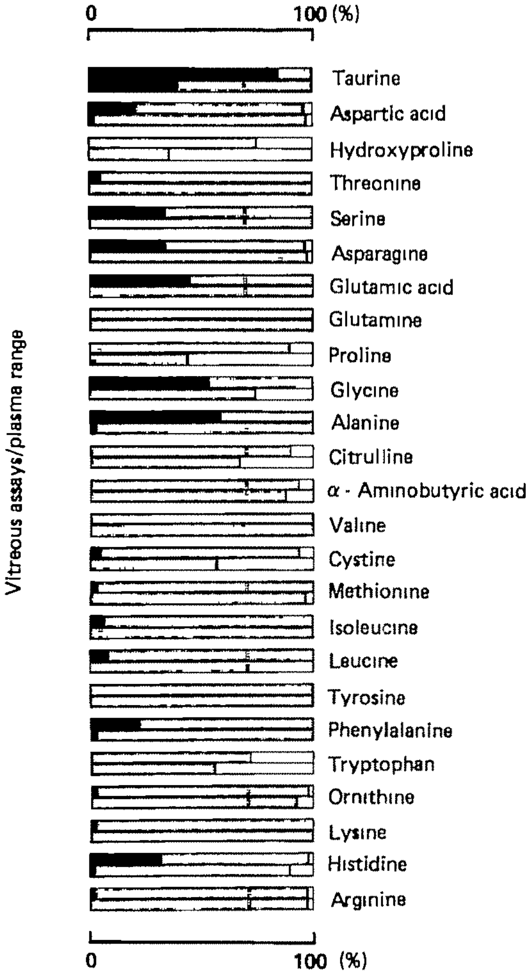

Fig 2 *Percentage of vitreous amino acid assays above (black) within (shaded) and below (white) the normal plasma range in over 24 hour (upper band) and under 24 hour (lower band) postmortem interval groups*

Discussion

Postmortem changes occur less rapidly in vitreous humour than in other body fluids so that theoretically at least analysis of the vitreous humour could give useful information regarding a possible cause of cot death.[6] Little is known about the progression of the biochemical changes after death so that in analysing such changes multiple variables should ideally be taken into account including for example feeding patterns, circadian rhythm, and latent infections, in addition to the parameters we have already considered.

The present study has indicated that samples should be obtained not more than 24 hours after death to give reliable results. The postmortem interval as already defined established fixed limits for the interval and avoided possible overestimation of the amino acid concentration relative to time after death

Analysis of the results showed no evidence that a specific aminoacidopathy is implicated in the aetiology of cot death but has nevertheless improved our understanding of the biochemical background of these cases.

The baseline data for vitreous amino acid concentrations by age and postmortem interval in cot deaths may be of value to other investigators and is presented in a table that is available from the corresponding author.

We should like to thank Mr F[illegible] S[illegible]m and Mr Peter McAllister who undertook the amino acid analysis, Mr Jim Ito for help with computer analysis of the results, Mr Fergus Coleman for preparing the illustrations, and Mrs R [illegible] for typing the manuscript

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Subcutaneous rheumatoid nodules

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SUMMARY We describe seven children with subcutaneous rheumatoid nodules who had no clinical evidence of rheumatoid arthritis. Only one girl was seropositive for antinuclear factors and had a slightly raised erythrocyte sedimentation rate. Clinical aspects, risks for developing rheumatoid arthritis, and treatment of this entity are discussed.

Subcutaneous tumours that histologically resemble rheumatoid nodules are rarely encountered in healthy children—that is, those without evidence of arthritis. Unfamiliarity with these lesions often gives rise to uncertainty concerning the subsequent—possible—occurrence of rheumatoid arthritis and the treatment of the frequently appearing recurrences. In this article we review our own data and compare it with results found in the literature.

Patients and methods

We reviewed the notes of seven children who had been referred to the department of paediatric surgery at the St Radboud University Hospital in Nijmegen between January 1970 and October 1986 with subcutaneous lesions, which were histologically undistinguishable from the nodules found in adults with rheumatoid arthritis. All children were invited to take part in a follow up examination. The response rate was 100%; the period of follow up varied from 6 months to 17 years (mean 6·3 years).

Results

At the first presentation to hospital all children were found to be healthy and none of them had a history of joint disease. Clinical details of the children are shown in the table. The group consisted of two boys and five girls, and their mean age was 5·5 years (ranging from 6 months to 10 years). A solitary nodule had been diagnosed in four children, one child had had two nodules, and two had presented with multiple nodules. Most lesions had been found in the extensor side of extremities: four pretibial, one prepatellar, one on the dorsum of the foot, and one on the extensor side of a finger. In two children the lesions had been situated on the scalp. The size of the nodules ranged from 2 mm to 4 cm. Ten of the subcutaneous nodules had been excised and histo-

Table *Clinical findings*

Case No	*Sex*	*Age (years)*	*Number and location of nodules*	*Length of follow up*	*Observations*
1	M	0 5	1, tibia	6 months	Recurrence*
2	F	2	Multiple scalp	6 years	Still recurrences
3	F	3	5, tibiae, dorsum of foot	17 years	2 recurrences†
4	F	4	2, scalp	11 years	1 year ibuprofen, no recurrence
5	M	8	1, tibia	9 months	Recurrence‡
6	F	10	1, finger	2 years	No recurrence
7	F	7	1, knee	7 years	Recurrence§

*=Recurrence still present at follow up

†=Recurrence after re-excision of recurrence, spontaneous regression

‡=Recurrence disappeared spontaneously

§=Recurrence re-excised, no recurrence This girl had a slightly raised erythrocyte sedimentation rate and was positive for antinuclear factor

logical examination showed them all to be 'rheumatoid nodules.' One child, a 4 year old girl, had used ibuprofen for one year after the lesions had been diagnosed. Local recurrences arose in four cases; one disappeared spontaneously within five months, another had not regressed during six months of follow up. The remaining two were re-excised. One recurred, but disappeared after six months. In one patient new nodules kept developing on the scalp during the six years after the first diagnosis had been made. These lesions always regressed within two months. All unexcised nodules resolved spontaneously after a period of one month to six years.

At the time of follow up, none of the children were found to have had arthritis or any related disease. There was no evidence of rheumatoid arthritis in their family histories. No pathological murmurs were heard at cardiac auscultation and no limitations of joint movement were observed. All laboratory tests (erythrocyte sedimentation rate, white blood cell count, antistreptolysin titre, antinuclear antibodies, Latex test, and Rose's test) gave normal results except in one girl who had a slightly raised erythrocyte sedimentation rate of 13 mm in the first hour and was positive for antinuclear antibodies.

Discussion

Over 200 children with this disorder have been described. Because of the histology and clinical behaviour of the nodules they have been referred to under several different names: benign rheumatoid nodule, pseudorheumatoid nodule, non-rheumatoid rheumatoid nodule, and subcutaneous granuloma annulare. The youngest patient described with this disorder was 11 days old.[1] Some authors believe that trauma causes the nodules because there was a history of trauma in 25% of their patients.[2] In our patients there was only one case where a prepatellar nodule could have been the result of trauma. Streptococcal infection has also been suggested as a causal factor.[3,4] These nodules are seldom painful, except in areas which are susceptible to pressure. They are mostly found on the limbs, scalp, and near the eyebrows.[1–4] Their size ranges from 2 mm to 5 cm They are nearly always joined to the underlying fascia or bones and multiple lesions are often observed. Preoperatively the diagnosis is often missed. The histological picture is identical to that which is seen in the subcutaneous nodules of adults with rheumatoid arthritis. They consist of a centre of fibrinoid necrosis surrounded by pallisading fibroblasts and histiocytes, deposited in granular tissue (figure). The clinical behaviour, however, is quite different.[5] These nodules develop in 20% of adults with rheumatoid arthritis, usually after the arthritis has manifested itself[5] They are mostly located on the proximal ulna, forearm, hand, pelvis, and foot. Rheumatoid nodules in adults are not painful either, but they do not regress spontaneously; their presentation implies a poorer prognosis. In children with juvenile arthritis, 6–9% develop subcutaneous nodules, but the histology is different: no central necrosis or pallisading histiocytes are encountered.[6]

Some investigators have evaluated the blood test results in these children, but no definite predictive factor for subsequent rheumatoid arthritis could be established.[3,4,6] One child has been described with a raised erythrocyte sedimentation rate and one other with positive tests for antinuclear factors at the moment the rheumatoid nodules were diagnosed: both later developed rheumatoid arthritis[4,6] Only one of our patients had abnormal laboratory test results (a raised erythrocyte sedimentation rate and a positive antinuclear factor) but no symptoms or

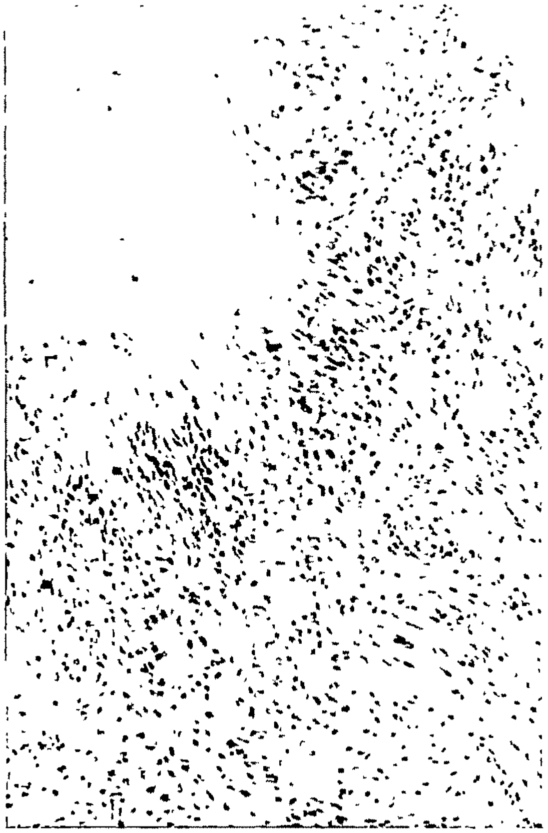

Figure *Photomicrograph showing part of a pseudorheumatoid nodule: fibrinoid necrosis surrounded by pallisading fibroblasts and histiocytes (haematoxylin and eosin stained, magnification × 200)*

signs of any rheumatoid associated disease could be found at the initial presentation or after seven years of follow up.

At least one biopsy specimen should be taken to make a proper diagnosis. If several identical nodules are present it is not necessary to excise them all unless they are causing trouble to the patient (for example, pressure areas). The nodules will regress eventually, without any treatment.[3 4] The same applies to the recurrences. Thus other forms of treatment such as, radiotherapy, corticosteroids or non-steroid anti-inflammatory medication (the latter was used in one of our patients) are superfluous and undesirable.[3-5]

The longest follow up period reported is 20 years.[3 4] One should keep in mind that these patients are still under 30 years old; rheumatoid arthritis usually manifests itself somewhat later in life. So far four children with rheumatoid nodules have been described who have developed rheumatoid arthritis between 2 months and 18 years after the initial diagnosis.[4 6] It seems unlikely that healthy children with rheumatoid nodules run an increased risk of developing rheumatoid arthritis later in life because the disorders have different predilection locations, the rheumatoid nodules in children regress spontaneously, and these children usually have normal blood test results. Once the diagnosis of rheumatoid nodules has been made, the parents should be reassured and their child can be discharged from follow up.

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Relation between height velocity and fasting insulin concentrations

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SUMMARY A linear relation between fasting serum insulin concentration and height velocity was found in 47 normal children This suggests that doubling of growth velocity at puberty is accompanied by a two to threefold rise in insulin. This implies that insulin dosage should be increased by a similar magnitude in pubertal diabetic children during their growth spurt.

It is widely accepted that good diabetic control leads to a reduction in the longterm complications of diabetes.[1] In children with diabetes this control has to be established upon the background of the changing endocrine milieu of growth and pubertal development. We have recently shown important changes in parameters of insulin secretion in association with puberty and concluded that changes in circulating growth hormone concentrations could produce these effects. In diabetics, changes in insulin dosage need to parallel these events and we now describe a simple relation between fasting insulin concentration and growth velocity that might be of value to clinicians looking after such patients.

Subjects and methods

Forty seven children (25 boys and 22 girls) aged between 4·2 and 16·4 years who attended the growth disorder clinic at the Middlesex Hospital were studied. These children were being investigated for disorders of growth and comprised tall and short, prepubertal, and pubertal children. The short prepubertal children were part of a cohort reported previously,[2] and the samples from these children were obtained during their (delayed) pubertal growth spurt. Standard auxological assessment was performed over one year.[3] The blood samples were obtained at the mid point of the yearly assessment to accord with standard reporting of height velocity. Blood samples for the measurement of serum insulin concentration were taken at 0800 hours after an overnight fast Plasma was separated immediately and stored at −20°C until measured using a double antibody radioimmunoassay [4]

The intra-assay and interassay coefficients of variation for the insulin radioimmunoassay were 3·6% and 9·6% respectively at serum insulin concentrations between 20 and 25 mU/l The sensitivity of the assay was 2·0 mU/l.

The relation between fasting serum insulin concentration and height velocity was investigated by linear regression and the calculation of Pearson's correlation coefficient. The possible contribution of age and stage of puberty were studied by stepwise multiple regression analysis

Results

Of the 47 children, 24 were prepubertal (seven tall, 17 short) and 23 pubertal (15 tall, eight short). The relation between fasting serum insulin concentration (y) and height velocity (x) is shown in the figure and described by the linear regression equation: $y=2{\cdot}1x-5{\cdot}8$ ($r=0{\cdot}74$; $p<0{\cdot}001$).

Introducing pubertal staging into the regression

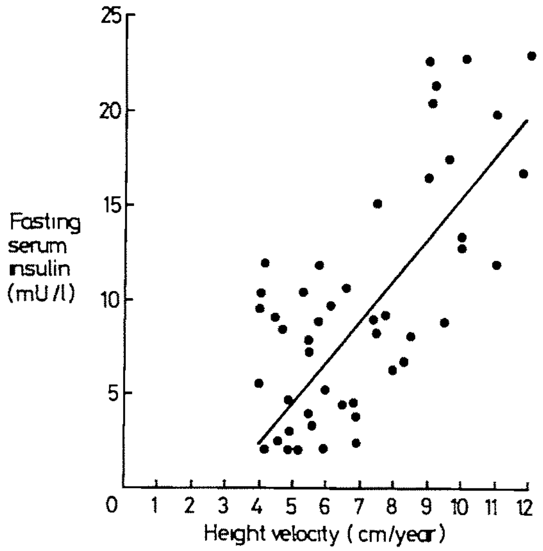

Figure *The relation between fasting insulin concentration and height velocity* equation increased r to 0·79. Age added little more (r=0·30)

Discussion

These data show a simple linear relation between height velocity and fasting serum insulin concentration. This association is probably indirect and secondary to changes in circulating growth hormone concentration. Growth in mid childhood is growth hormone dependent while that of puberty results from synergism between growth hormone and circulating sex steroids.[2] [5] High circulating concentrations of growth hormone are known to increase fasting insulin concentrations and to promote insulin resistance at peripheral tissues.[6]

The model proposed supports the observation of an increase in serum insulin concentrations associated with puberty. It suggests that a two to threefold rise in fasting serum insulin concentration occurs as a result of a change in growth velocity from pubertal values of about 5·5 cm/year to that seen during the pubertal growth spurt of 10 cm/year or more. These data may have importance for clinicians caring for pubertal diabetic patients. If the findings of this study were extrapolated as an index to total daily insulin requirement, such patients might need up to a threefold increase of insulin dosage to maintain euglycaemia and an acceptable growth spurt. As growth hormone secretion decreases after puberty it is possible that insulin requirements will also fall in adulthood.

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Prepubertal hypertrichosis: normal or abnormal?

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SUMMARY The pattern of hair growth, morphology of the hair shafts, and the hair root state are described in four girls and two boys with prepubertal hypertrichosis. The exact nosology of this form of excessive hair growth is discussed in relation to hirsuties and the possibility of it representing an 'atavistic' trait.

Hypertrichosis in childhood may be seen in a variety of congenital and metabolic disturbances, after administration of therapeutic agents in utero, and after birth and in association with chronic disease.[1] In most of these disorders the excess hair growth is not considered to be a major component and is usually noted only for completion. In contrast, most cases of hypertrichosis lanuginosa have been reported because the excess hair growth is the primary disorder.

We report a series of children with hypertrichosis as this pattern appears to have been ignored or, conversely, given the diagnostic label of hirsuties: the latter is a diagnosis that suggests an aetiology of androgen hormone excess.

Case reports

Six children with noticeable congenital generalised hypertrichosis were seen. There were two boys (ages 3½ and 7¼) and four girls (ages 2¾, 6, 6½, and 8). Two boys and one girl were Asian; one of the other three girls had a Celtic father, the other parents were Anglo Saxon. Five of the children had dark hair and only one had blonde hair. Five of the children had no family history of excess hair. One of the girls had a brother with 'hairy elbows ' All the children had normal physical and mental development and were entirely healthy. None of the children had been exposed to drugs known to cause hypertrichosis either in the prenatal or postnatal periods. Only the four girls presented with the problem of excess hair, one of the boys was seen when he attended a dermatology clinic with his brother, the other was coincidentally seen with insect bites.

PATTERN OF HAIR GROWTH

The pattern of hair growth was similar in all cases, although there were varying degrees of severity. In the two boys, there were sparse fine pigmented hairs around the root of the penis but this was not progressive In none of the other cases was there any suggestion of axillary or pubic hair development. The external genitalia were normal and appropriate for the age of the children and there was no breast development in the girls. The pattern of hair growth was as follows

Face

There was a dense growth of terminal hair over the scalps, which had a low anterior hair line This was particularly noticeable in the temporal regions where the scalp hair merged into bushy eyebrows. The faces were covered with fine but densely pigmented hair (fig 1).

Trunk

The hair was more pronounced over the back and there was only minimal growth on the front of the chest and abdomen The hair streams flowed around the sides of the chest to the back, met in the midline and continued towards the sacrum, and gave an appearance of an inverted fir tree In three of the children a whorl was present overlying the spine between the scapulae (fig 2)

Limbs

The arms and legs were covered with long hair shafts which had the nature of thick, coarse, and curly terminal hair, these differed from other sites which were covered with vellus hair. This was appreciable on the legs and at the elbow region where the hair growth was profuse

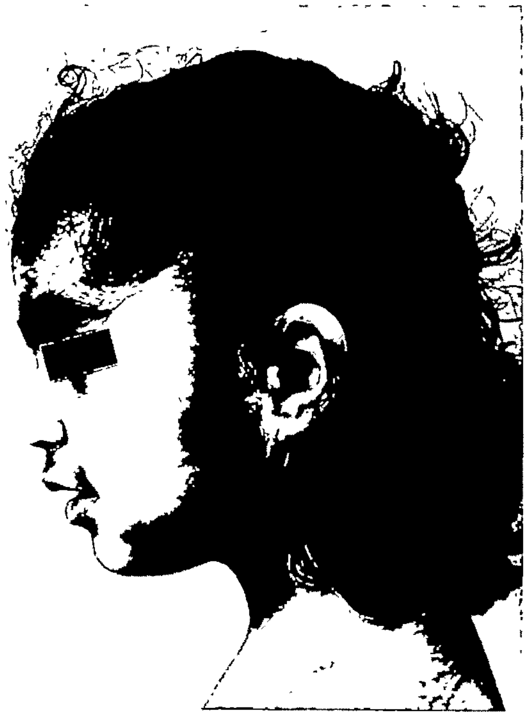

Fig 1 *Lateral view of the face and shoulder of the Asian girl showing bushy eyebrows and hypertrichosis on the forehead, side of the face, ear, and shoulder*

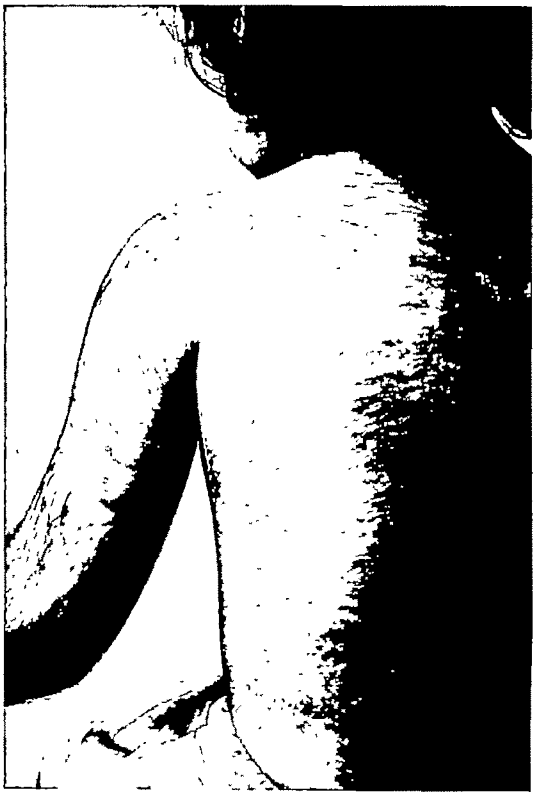

Fig 2 *Later view of the trunk of the Asian girl showing hypertrichosis of the back and shoulder, and dense growth on the arm particularly around the elbow*

EXAMINATION OF HAIR

Hairs plucked from the upper back and either thigh or elbow region were examined by light microscopy. In all cases, the hair shafts had normal morphology with well formed medullas. Examination of the hair roots showed both anagen and telogen bulbs from all sites; unfortunately, many hairs had fractured above the roots preventing an accurate assessment of the ratio of anagen to telogen bulbs.

Discussion

The pattern of hair growth in these otherwise healthy children is quite unlike that seen in hirsuties. Hirsuties is the pattern seen in adults with cutaneous or systemic virilism; it is only seen in children suffering from virilising disorders—for example, congenital adrenal hyperplasia or hormone secreting tumours. In hirsuties the hair growth is predominantly on the upper lip, chin, abdomen, and inner thighs.

The main difference between the hypertrichotic pattern described in this report and hirsuties was the hair growth on the face and trunk. The described facial hair pattern was dominated by bushy eyebrows, a low frontal hairline, and a hairy forehead. The hair on the trunk was predominantly on the back and extended to the shoulders and upper arms: both these sites are the last to be affected in hirsuties. The hair shafts on the face and trunk in hypertrichosis are fine, silky, and straight whereas in hirsuties they are thick, coarse, and curly.[2]

Such a detailed description of the pattern of hair growth has only been given in a single previous report of uncomplicated hypertrichosis.[3] Other reports in the paediatric and genetic literature are difficult to interpret because of the seemingly interchangeable use of the terms hypertrichosis and hirsuties.

The aetiology of this form of hypertrichosis is obscure. It has been suggested that body hair is an 'atavistic relic'.[4] This concept, however, is not supported by detailed observations of hair patterns in many species of animals, including primates, all of whom have completely different patterns,[5] the most prominent being the direction of hair growth on the back. In animals the hair grows from the midline towards the belly so that, in a quadruped, the hair acts as a watershed; in hypertrichotic children the direction is reversed.

It is often held that 'racial hirsuties,' which is probably identical to the hypertrichosis described above, is common among Asians.[1] It is clear from this report, however, that hypertrichosis does occur in white children, although it may appear to be more prevalent among Asian children as their dark hair is more noticeable. The relative absence of body hair in the Mongoloid races further confirms that racial differences do occur.[6]

It is unknown if the pattern of hypertrichosis described represents an abnormal entity or whether it occurs as an extreme form of the normal range of hair growth. Larger population studies of children will be required to determine this issue.

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Budd-Chiari syndrome treated by Senning operation

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SUMMARY Budd-Chiari syndrome was diagnosed in a 13 year old boy who presented with ascites Angiographic studies showed occlusion at the ostia of the hepatic veins. This was treated surgically by the Senning operation of transcaval dorsocranial resection of the liver and hepatocaval anastomosis. The patient's ascites cleared and he remains well 10 months after surgery.

Budd-Chiari syndrome is characterised by hepatic venous outflow obstruction. The obstruction may occur at any point from the efferent vein of the hepatic lobule to the supradiaphragmatic part of the inferior vena cava. In Parker's review of 115 cases of idiopathic Budd-Chiari syndrome 44% were associated with occlusion of the hepatic vein ostia, but most cases also had distally situated lesions.[1] Although in many instances the aetiology is obscure. certain causes are well known These include thrombotic disorders such as polycythaemia, oral contraception. systemic lupus erythematosus, and paroxysmal nocturnal haemoglobinuria. Tumour invasion of the hepatic veins and inferior vena cava—for example, by Wilms' tumour—is well recognised. Webs in the inferior vena cava, presumably congenital, cause membranous intraluminal obstruction Veno-occlusive disease of the liver associated with drinking bush teas is a relatively common cause of the syndrome in certain parts of the world Budd-Chiari syndrome may be a sequel to blunt abdominal trauma such as road traffic accidents. Constrictive pericarditis may present as Budd-Chiari syndrome.[2]

The potential for corrective surgery is limited to those cases where a discrete distal anatomical lesion such as a congenital web in the inferior vena cava is found.[3] Senning has devised a technique of transcaval dorsocranial resection of the liver in cases of juxtacaval hepatic vein occlusion.[4] We describe a 13 year old boy who presented with Budd-Chiari syndrome secondary to hepatic vein occlusion who was successfully treated by a Senning procedure.

Case history

This 13 year old Asian boy was referred with a two month history of ascites. He had been well apart from a road traffic accident six years previously when he was knocked down by a car and struck in the abdomen and legs. He presented as a thin boy, his weight was 34 kg (10th centile), his height 142 cm (10th centile) He was not jaundiced and there were no signs of chronic liver disease. Abdominal examination showed gross ascites and 3 cm hepatomegaly. The differential diagnosis at time of admission was tuberculous peritonitis, malignancy, or chronic liver disease

Results of initial investigations included haemoglobin 12·3 g/l, erythrocyte sedimentation rate was 1 mm in the first hour, prothrombin ratio 1·5. The results of liver function tests were. bilirubin concentration 24 μmol/l, alanine aminotransferase activity 27 IU/l, and alkaline phosphatase activity 399 KAU/l. Albumin concentration was 40 g/l. Diagnostic paracentesis of the abdomen showed a protein content of 28 g/l, no organisms or malignant cells and no acid fast bacilli. Mantoux test 1/10 000 was negative A computed tomogram of the abdomen showed ascites but no evidence of an intra-abdominal mass He then had an exploratory laparotomy at which 600 ml of ascitic fluid was removed The liver was swollen, hard, and micronodular Histology of an open liver biopsy specimen taken at laparotomy showed centrilobular distention and congestion consistent with early Budd-Chiari syndrome.

Abdominal ultrasound examination showed ascites, normal liver texture, and patent hepatic veins An echocardiogram showed normal cardiac structure and function with no evidence of pericardial constriction. An inferior venacavogram via the left femoral vein was performed during which the catheter passed freely from the inferior vena cava into the right atrium thus excluding a web in the inferior vena cava. Contrast injection showed side to side narrowing of the intrahepatic part of inferior vena cava. Transcatheter pressure measurements made above and below the narrowing showed a pressure gradient of 10 cm of water. The hepatic veins could not be entered and on contrast injection there was no retrograde filling of the hepatic veins Only a small cluster of veins in the caudate lobe could be opacified (fig 1). The appearances were interpreted as showing hepatic vein occlusion and extrinsic compression of the inferior vena cava. This was confirmed by percutaneous transhepatic

Fig 1 *Lateral view of inferior venacavogram showing local concentric narrowing of intrahepatic part of the inferior vena cava*

venography. Contrast injected into the liver parenchyma from the right axilla using a 22 gauge needle outlined normal branching hepatic veins in the right and left lobes. Flow was sluggish and the hepatic veins were occluded at their ostia (fig 2)

Management of the ascites included salt restriction to 20 mmol/day and fluid restriction to 800 ml. Diuretics were given as spironolactone 100 mg three times a day and frusemide 30 mg daily. The prothrombin ratio increased to a maximum of 2 5 and was treated by injections of vitamin K. Serum albumin fell to 27 g/l and was maintained by intermittent infusions of salt poor albumin.

He then underwent a Senning operation. The heart was exposed via a median sternotomy incision and he was placed on cardiopulmonary bypass The abdomen was opened to the umbilicus Several litres of ascitic fluid were aspirated and both lobes of the liver were seen to be grossly congested The diaphragm was split vertically and the inferior vena cava was dissected until it disappeared into the liver. The inferior vena cava was opened longitudinally starting in the supradiaphragmatic portion and carried down into the liver. Dissection of a vertical incision into the liver substance and excision of liver tissue anterior to the caval wall allowed the identification of hepatic radicles in the right and left lobes. These were difficult to identify owing to considerable fibrosis and thickening of the surrounding liver tissues These venous radicles were opened up with probes and immediate drainage of large quantities of blood resulted with considerable decompression of the liver. A hepatocaval anastomosis was then performed opposing the liver to the cardiac end of the inferior vena cava. The inferior vena cava was closed transversely by continuous suture so as to widen the cava immediately above the liver

Postoperative recovery was uneventful Liver function tests, albumin concentrations, and prothrombin ratio returned to normal values The patient remains well, and is free of ascites and off all medication at follow up 10 months after surgery.

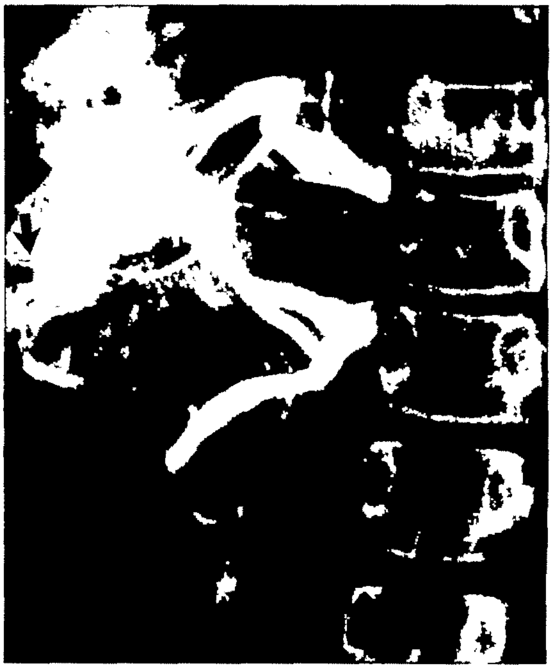

Fig 2 *Percutaneous transhepatic venography Parenchymal contrast injection into right lobe (arrow) showing patency of intrahepatic veins and occlusion at ostia of the hepatic veins*

Discussion

Diagnosis of chronic Budd-Chiari syndrome should be considered in patients presenting with ascites, hepatomegaly, and normal or mildly deranged liver function tests. The diagnosis may be suspected if a technetium colloid liver scan shows decreased hepatic isotope uptake, except in the caudate lobe where uptake may be normal or increased; or if hepatic veins with normal blood flow, as shown by Doppler imaging, cannot be identified on ultrasound scanning Definitive diagnosis is made by a liver biopsy specimen showing the characteristic appearance of centrilobular sinusoidal distension

Patients with chronic Budd-Chiari syndrome are a heterogenous group because of its multifactorial aetiology, and prognosis for individual cases is variable. The overall prognosis is poor with a five year survival of 20–50%. A recently reported series associated poor prognosis with malignancy, paroxysmal nocturnal haemoglobinuria, hepatic failure, and portal hypertension[5] A better prognosis was associated with remediable causes such as surgically treatable webs in the inferior vena cava.

The angiograpic techniques of cavography and percutaneous transhepatic venography allow the vascular pathology of chronic Budd-Chiari syndrome to be localised precisely.[6] Other reports have emphasised the potential for surgical management of inferior vena cava webs.[3] Previously the prognosis for patients with hepatic vein occlusion was poor but the Senning procedure offers treatment for this group.

The aetiology of this boy's hepatic vein occlusion is uncertain The collagenous reaction which occluded the hepatic veins may have been secondary to trauma sustained in a road traffic accident. The present case shows the value of full angiographic study of patients with chronic Budd-Chiari syndrome as localisation of the site of obstruction may allow remedial surgery.

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Current topic

Prevention of mental handicap and developmental disabilities in South East Asia

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Commonwealth Association for Mental Handicap and Developmental Disabilities

The National Population and Family Development Board, Malaysia, in association with Malaysian Paediatric Association and Commonwealth Association for Mental Handicap and Developmental Disabilities (CAMHADD) held a workshop in Kuala Lumpur in September 1986 on prevention, early detection, and intervention of childhood handicap. The main objective was to identify those problems for which practical programmes of implementations, with special reference to Malaysia and other South East Asian countries, could be initiated. The workshop was attended by 30 invited experts on mental retardation from South East Asia and other Commonwealth countries. During the two days various aspects of mental retardation were discussed and the following recommendations were made.

1. Prevalence and early identification of developmental disabilities and mental handicap

Developmental disabilities and mental handicap present a problem that must be recognised in all parts of the world. In order to plan services for those affected it is essential that well designed data collection systems should be used to determine the prevalence and causes. A general screening test for developmental delay will detect most disabilities but it may miss some impairments such as functionally important hearing loss or squint. There is, therefore, a need to develop simple tests, appropriate for each community, for those specific impairments for which treatment is available. The tests would require careful evaluation before using them with general screening.

2. Health education and professional training

A greater public awareness of child health and development is needed. All available news media should be used to give practical information about normal development and warning signs particularly to parents, children at school, community workers, and teachers. Health professionals need special training in child development and the identification and management of disabilities. Special workshops should be set up for those who will be responsible for training.

3. Jaundice of the newborn

Bilirubin encephalopathy is a preventable cause of mental handicap and is a particular problem in South East Asia because of a high incidence of an inherited disorder, glucose-6-phosphate dehydrogenase deficiency. Cord blood screening by enzyme test should be performed on *all* infants at birth and the results reported promptly. It would then be possible to eliminate brain damage in this condition using light treatment and health education to avoid exposure to toxic substances such as mothballs and herbal medicines. Parents and health workers should be made aware of the serious consequences of neonatal jaundice

4. Implementation

Because of the well developed child health services in Malaysia it is proposed that study groups should be set up in that country to implement these recommendations. CAMHADD could then use the Malaysian experience for extending similar programmes in other developing countries.

5. Prevention of mental handicap

Increasing attention needs to be given to antenatal care. particularly to the identification of high risk pregnancies and the selection of women for home delivery. Immunisation against a number of infectious diseases—for example, tuberculosis, rubella, measles, and polio—will reduce brain damage or major disabilities. Therefore every effort should be made to ensure that children have the benefit of these immunisations. Accidents are an increasing cause of brain damage in childhood; major efforts need to be made to reduce their frequency and the death and disabilities which result from them The recommendation on genetic counselling made at the Bombay workshop[1] that genetic services, appropriate for each country, should be available in the developing countries, was re-emphasised.

6. Early intervention and education

It is the right of *all* handicapped children to be given appropriate education so that they achieve their maximum potential. Parents should be encouraged to involve themselves in the education of their children. In addition self help groups have an important part to play It is preferable to initiate intervention programmes early in the child's life in order to reduce subsequent handicap.

The Workshop felt that because the child health services in Malaysia were well developed, it should be possible to implement most of the recommendations in Malaysia and to extend the experience so obtained to the neighbouring and other developing Commonwealth countries.

This workshop would not have taken place without the generous grant from the Commonwealth Foundation and the British Council The local organisation was under the directorship of Dr Ali Halim

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Archives of Disease in Childhood, 1988, **63**, 674–677

Personal view

Community paediatrics: anxieties on future developments

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Since working in the community as a clinical medical officer I have had to alter a number of my ideas and beliefs built up over 25 years as a 'hospital doctor' even though I had regular clinics in special schools. In retrospect I realise my concepts of problems in the home, school, and community were limited and sometimes unrealistic. After working in school and community clinics for a few years I have come to recognise the expertise that is needed to provide an effective service to preschool and schoolchildren.

For those working among preschool children a detailed knowledge of developmental paediatrics is essential. Testing for the normal development of vision, hearing, and language in young children is often difficult, and special training is needed if reliable results are to be obtained. The complexities and uncertainties are well illustrated by a review of screening tests for squint and poor vision by Taylor.[1]

When I used to see a number of so called clumsy children at the age of 10 or 12 they often fitted into my 'if only syndrome.' If only someone had done something about it a few years earlier it is probable that many of the present problems would not have arisen. It is not always easy, however, to assess the importance of failure of motor tasks at an early age. This may be due to specific learning difficulty but social and emotional factors may well play a part; and considerable experience is needed in sorting out an often complex condition. Disorders and delay of language development are also diverse in cause and effect. Such disorders are frequently associated with abnormal behaviour and these children are often referred to the school doctor. The children more at risk of being neglected are those who are labelled as very quiet in the nursery school because they say nothing, and some have little ability to do so, but cause no one any trouble. Some have deficiencies of social skills out of proportion to their language deficits.

In a recent review of outcomes of a random 1:7 sample of 1700 school entrants born in 1980 in the Macclesfield health district it was found that 14% of the pupils had conditions previously undiagnosed, which warranted referral (C Jones, personal communication). Deafness was one of the most frequent disabilities found. Yet diagnosis and treatment of deafness in early childhood can make a very important difference to a child's development. Fifteen per cent of the parents indicated on a questionnaire that there were problems they wished to discuss at the time of the examination and 9% had their concerns confirmed. Also of importance is discussing a particular child's difficulties with the teacher and school nurse as soon after the start of school as possible. This emphasises the need to establish a good working relationship which can only be achieved by meetings on the school premises. There are arguments on the timing of the school entry examination[2] and how selective it should be.[3] With limited resources, which are not likely to improve in the immediate future, there are strong reasons for concentrating the doctor's work on the neurodevelopmental examination and on certain aspects of the physical examination (for example, heart, chest, testes), and on children with appreciable growth and sensory problems found on screening tests done by paramedical personnel.

Now that there are more handicapped children, and even those with severe disabilities, attending primary and secondary schools, accurate assessment of the child's condition is even more important. If this is done at an early age plans can be made for providing any suitable help especially if there is progressive disability. The doctor working with handicapped children, whether in mainstream or special schools, must have adequate knowledge of paediatrics and related specialties. This knowledge should include what is known about the causes, natural history, and treatment of conditions, and when applicable the genetic implications. It is still surprising how often parents and older children have not been offered genetic advice. Twelve out of 70 pupils in a Salford special school were found with identifiable genetic disorders who had not been offered advice (I McKinley, personal communication). (They included children with congenital eye defects.) Referral to a clinical geneticist is usually required.

Often the families of handicapped children need skilled advice from several disciplines and this should be coordinated in the community. Realistic goals can be set with knowledge of home and family circumstances. Adequate resources and time must be devoted to this work

At primary school many problems can arise that need expert attention and these often need to be discussed in detail with both parents and teachers. These include failure to acquire motor skills at the expected age and disorders of language development including all aspects of literacy with the implications of these for learning in general. Clumsy children can sometimes lead very unhappy lives at school.[4] Assessment and management of children with learning disabilities needs the aptitude to work as a member of a team, and as a coordinator when appropriate, as well as a knowledge of learning disorders. The doctor working in the school is at an advantage when it comes to involving health professionals (therapists, nurses, orthoptists, audiometricians, dietitians, chiropodists, dental services, general practice, and specialist medical services). Advice for teachers will be needed on children with visual and auditory problems and long term disorders such as asthma, diabetes, and epilepsy.

I have been impressed recently by the number of children showing evidence of nasal obstruction and suffering as a result of this. Apart from breathing through their mouths and snoring at night their school performance may deteriorate because they are so sleepy during the day.[5] This information may only be available from their teachers, and no doubt there are other examples of conditions that could be improved as a result of collaboration between teachers and doctors.

If teachers are involved in the management of children with long term disabilities, especially those with epilepsy, this improves the lot of the affected child and the understanding of peers. This is only possible, however, if the teacher has reasonable knowledge which is likely only to be available from the school doctor. Several children have been referred to me by teachers who have been the first to notice petit mal. One of these children was obviously having non-convulsive status epilepticus, although the mother had been told there was nothing to worry about

Close links will often have to be made with educational welfare, child guidance, and social services when dealing with emotional and behavioural disorders, including the management of children at risk from physical, sexual, and mental abuse. Helping these children is time consuming and needs knowledge of how to recognise the suffering child, the best approach to child and parents to avoid doing more harm than good, and how to cope with follow up. These and other problems can be included under the term 'educational medicine', as they may all possibly interfere with the child's learning in school.

When it comes to secondary school education a particular skill is also required by the doctor concerned in trying to help with the complex emotional and behavioural disorders which can develop at this time of life. These include deficiencies in social skills, excessive anxiety or withdrawal, a variety of sexual problems, and all the complications of drug and solvent abuse. School doctors can assess and give primary care to these children before deciding on the need for psychiatric opinion,[6] but this requires a degree of experience and training which at present relatively few doctors possess.

I was certainly impressed recently when attending a clinic in a secondary school run by a (women) senior community medical officer. The problems presented by the children were varied and complex, and although I thought that many of the girls would come and tell her their troubles I was surprised how often the boys did too. A school nurse can be a key figure in the secondary school and a number are, but I am amazed how often such schools do not have a nurse in attendance for long periods. The teachers and pupils need to see the doctor and nurse often enough to known who they are and to be willing to talk to them.

If intervention is to be successful sufficient time and commitment is essential, and the doctor recognised as a colleague by the school staff is at a particular advantage. Anyone who dismisses the importance of this work and of other tasks such as immunisation does a disservice to children, because the potential for prevention of disabilities and minimising their effects is great Before working in the community I had not realised the extent of this work. Had I known I feel sure that my work as a paediatric neurologist would have been more effective. (This is the motivation for writing this paper, particularly with the anxieties over the plans for the future development of community services.)

Uniformity in planning services should be questioned Needs and circumstances of children vary widely—for example, between a self contained rural community and an inner city area. Solutions may require maintaining a number of options

A major problem is the relative lack or equivocal outcome of research in community health. Policy decisions can be taken on financial grounds by people who have little direct, practical knowledge of this work. Abolishing the 'third force' and dividing medical provision for children in the community between the general practitioner and consultant paediatrician may not be a desirable development in all areas of the country. Community paediatrics lays a great deal of stress on preventative medicine which inevitably entails a lot of routine work. In discussions a distinction must be made between screening and health surveillance. The former is the identification of disease in a population and in the latter the concern is the health and development of a unique child; and this difference is not always made.[7] Routine examinations do identify a variety of conditions from undescended testes to heart murmurs and defective sensory input channels but more information is needed on the cost effectiveness, sensitivity, and specificity of these exercises.

There is still controversy over who should test, particularly in screening tests and at what age they should be carried out Hopefully establishment of consultant posts in community child health will facilitate studies to clarify the role of the school nurse and the doctor giving primary care What is not in doubt is the need for all practitioners to be well trained, and in the case of those not medically qualified, they must be adequately supervised and willing to refer children with particular problems when these occur. There are questions of responsibility if errors should occur

Concentrating primary care for children in general practice should be evaluated by pilot studies. In many areas this may work well as the doctor will know the families, which is often so important, and can prescribe when necessary. When the administrative boundaries of education and health are roughly the same there should not be organisational problems, but in large conurbations with mobile populations this may well not be so. Also there must be an adequate number of doctors interested in community paediatrics and adequately trained. Even more important is their commitment to the work, for example it seems essential that the clinics must be held in the schools and not in the surgery so that there can be full cooperation with teachers who are directly involved with the child's progress

Whitmore stresses that to be effective the school doctor must visit each of his schools at frequent intervals.[6] In many areas this may be unrealistic for a long time to come but the reasons he gives are certainly persuasive. They include making a comprehensive check on the health and development of each child on school entry; discussing the results of this examination with parents and teachers; offering advice as seems necessary, on the child's continuing health care and education, examining or interviewing children, or both, on request and at a stated time soon after starting at secondary school; offering to organise treatment for any physical or developmental disorder found on examination, and being an accessible source of advice and support to the school nurse in her contribution to an agreed programme of health surveillance and health education. Bax has pointed out that during term time the school child spends more time with teachers than parents, and if the doctor who is trying to help cannot visit the child's school this is likely to limit the role he can have.[8] He may be unable to assess the child's needs and to integrate the medical aims with those of the teachers. This inevitably takes up a lot of time and may not be possible for general practitioners who are already hard pressed by the other calls on their services

To maintain the help that children so often need it seems that, particularly in cities, the work of the clinical medical officer should continue, at least for a considerable time If this is so there will be some community medical officers who will work from group practices, but some may wish to remain independent as they did not enter the field of community paediatrics to be part of the general practitioner services but to advance to a higher grade in community paediatrics This seems a reasonable ambition and in my opinion such a career structure should be maintained. Also some part time posts should be kept, despite administrative difficulties, to enable those with special skills to continue working while their own families grow up

Few would disagree that community paediatrics should be consultant led, and that with few exceptions future senior community medical officer posts should be regraded at this level, with the appropriate experience and training that this implies There are problems to be solved in the grading of those at present in post, and there are many such doctors who have an exceptional expertise to offer and do not wish to undertake the necessary training and examinations to be a consultant. It would therefore seem reasonable to allow some of these posts to continue at a non-consultant grade, perhaps on a personal basis.

It is obvious that any consultant paediatrician working in the community must have a major commitment to the community services. There are arguments favouring the involvement of consultant community paediatricians in acute paediatrics and of their being in charge of hospital beds but by the nature of the work acute paediatrics must take priority at times over all other duties, and time must be allowed to keep up to date with the rapid advances in this field There may well be advantages in being in charge of some beds in hospital so that a child can be admitted for medical or social reasons, but not being on any rota. Although the number of beds allocated to a particular consultant is no longer the status symbol it used to be, an involvement in the work of the hospital wards may help to place the consultant community physician on an equal footing with other colleagues. There are certainly a number of precedents for such an arrangement

The concern of those already working in the community seems to be the danger of acute paediatrics being the main interest, with community paediatrics being a secondary one, while among hospital based paediatricians who may not realise the full variety of work involved there may be a feeling that this is a perfectly rational arrangement Perhaps the strongest argument against an involvement with acute paediatrics is the amount of work that needs to be done in the community and the attitudes that have to be developed if this work is to be successful.

If standards are to be maintained and improved and people of the calibre needed are to be attracted to community paediatrics it is essential to establish better training, better conditons of work (at present often fragmented and carried out in unsatisfactory circumstances), a better career structure, and better facilities for research. The interests of doctors differ considerably. Whether they are general practitioners or consultants they will have concentrated their training in different ways. For example there is no guarantee in a group practice that one member wants to be involved in paediatrics. Opportunities for training in community paediatrics are not the same in all parts of the country and there is no doubt that training others takes up a lot of time of people who are already hard pressed by service duties.

In summary, my concern for the future is that, accepting that reorganisation is needed, this may lead to a loss of commitment to community paediatrics and a loss of some of the skills developed over the past few decades. If improvements do not occur it is the children who will suffer. Managers must be convinced by those with practical experience that depriving children of such services will in the long run be a false economy. Changes must not only serve the interests and claims of the doctor but must first of all be able to answer the question in the affirmative: does it help the children? If the needs are so variable, a number of options must be maintained

Thanks are due to Dr Martin Bax, Dr Ian McKinley, and Dr Kingsley Whitmore for their very helpful comments

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Correspondence

Cerebral blood flow velocity variability in infants receiving assisted ventilation

Sir,

We read the article by Rennie *et al* with great interest[1]

In the absence of any recording of blood pressure it is not possible to say whether perturbations in cerebral blood flow velocity result from transmission within the arterial system, or from the effects of changes in cranial venous volume, which are also known to affect it.[2] Unfortunately, as these different effects tend to be opposite in direction and out of phase with each other, it is not possible to distinguish between them by an analysis of cerebral blood flow velocity and respiratory phase alone The lack of distinction between the two effects is underlined by a failure to find a difference in the coefficient of variation expressed as a percent (CV%) of the spectrum area between the apnoeic and synchronously ventilated groups. This is the more surprising as it is known that the effects of passive lung inflation *v* spontaneous inspiration on left ventricular output and intracranial venous volume are not only opposite in direction, but also quite different in magnitude Our own work suggests that the CV% is inaccurate at low levels of variability such as those encountered during muscle paralysis and ventilation[3]

Another potential inaccuracy in the use of the CV% of the spectrum area lies in its reliance on the relative frequencies of respiration and heart rate; if spontaneous respiratory effort is occurring irregularly or infrequently, then the duration of 10 cardiac cycles may not be sufficient to quantify the effects of this activity on cerebral blood flow velocity. We have found good correlation between the CV% over 20 cardiac cycles (used in Perlman's original work) and an estimate of respiration induced variability using spectral analysis, at least in aortic blood pressure, during spontaneous respiration.[3]

Perhaps the most important effect of any treatment designed to stabilise the pattern of respiration in the first days of life is to prevent episodes of crying, Valsalva manoeuvres, and pneumothoraces which can affect both intracranial venous volume and arterial blood pressure adversely

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Drs Rennie and Morley comment·

We thanks Drs Bignall and Rivers for their interest in our paper Our present system allows the collection of only six seconds' worth of Doppler information, which was the reason for choosing 10 cardiac cycles, but the spectrum generated was from a fast Fourier transform and a Duplex system, which may bear more relationship to velocity than the continuous wave system used by Perlman and Volpe[1] While accepting that the area under the curve measured with computer assisted planimetry is a relatively crude index of variability the method was sensitive enough to detect differences between synchronous and asynchronous ventilation and the values for variation are in good agreement with other estimates of variability in systemic arterial pressure[2] We feel that the protocol, in which each infant acted as his or her own control and the velocity was measured with exactly the same technique in both types of ventilator interaction, adds confidence to what was a highly significant result ($p<0\cdot001$).

Further work is undoubtedly required on the underlying causes of variability and its accurate detection, and on the possible benefits of non-triggered synchronous ventilation Changes in central venous pressure are important and have been shown to occur sometimes opposite to the systemic arterial pressure swings, meaning that the changes in cerebral perfusion pressure are more marked[1] We plan to study this interesting phenomenon further with an improved method allowing rapid computer estimation over several minutes.

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Management of sexual abuse

Sir,

Drs Hobbs and Wynne stress the importance of reflex anal dilatation as a sign of anal sexual abuse.[1] In their reply to Dr Robert's scepticism concerning the reliability of the observation, they state 'We hold by our view that reflex dilatation of the anus correlates highly with continuing abuse , and is not found in diseases such as thrush, threadworms, or constipation' While not wishing to dispute this statement entirely, we do not believe that reflex anal dilatation occurs exclusively in cases of sexual abuse.

In a recent experience at this hospital, a 7 year old boy was admitted with non-specific abdominal pain, vomiting, and perianal soreness Physical examination showed reddening of the anus, an anal fissure, and marked reflex anal dilatation, a diagnosis of sexual abuse was considered on the basis of these findings There were no other features to support the diagnosis, however, and the child seemed a cheerful, well adjusted boy who enjoyed an excellent relationship with his parents.

Before voicing our suspicions, further questioning showed recent onset of mild diarrhoea containing mucus A barium follow through examination subsequently showed extensive changes of Crohn's disease in the terminal ileum Colonoscopy confirmed mucusal ulceration in this region, and histology of a biopsy specimen was consistent with Crohn's disease. The child was started on an elemental diet, and his symptoms and signs resolved quickly

Drs Hobbs and Wynne point out that they never base their diagnoses of abuse on the anal dilatation reflex alone. but in conjunction with other signs of anal damage such as '. . . fissures, veins, thickened perianal skin, scars ', etc.[1] These abnormalities, however, are all common findings in the 46% of children with Crohn's disease who have anal involvement at time of presentation.[2] Presumably, reflex anal dilatation occurs in some of these children in response to the pain often associated with perianal lesions in Crohn's disease

This case emphasises the importance of not relying on anal signs alone when diagnosing child sexual abuse. Crohn's disease occurs in approximately 1 child per 10 000, and, although uncommon, does appear to be increasing in incidence [2] It would, therefore, benefit paediatricians and general practitioners to bear the condition in mind when diagnosing child sexual abuse on the basis of abnormal anal findings.

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Anal dilatation and anal dilatation reflex associated with severe haemorrhagic colitis

Sir,

There is no doubt that dilatation of the anus and the anal dilatation reflex can be associated with penetrating anal abuse Recent controversy has focused on these two features, particularly the latter, among the many manifestations of child sexual abuse Clearly doubt exists regarding the validity of these two signs as sole indicators of anal sexual abuse in children They have been described also in Crohn's disease[1] and constipation (the passage of a very large formed stool) [2] It remains part of the controversy whether other local irritant or inflammatory conditions such as threadworm and rectal candidiasis can be associated with these signs [2 3]

We recently admitted a toddler, aged 13 months, with a three day history of watery diarrhoea For the two days before admission his stools were bloody and frequent, he was lethargic and unwell but not febrile He had not received any medication, and his parents denied administering rectal preparations or using rectal thermometers His bowel motions had previously been regular and soft, without pain or bleeding

On examination the perianal skin was reddened, and the anus was 2 cm patent, showing red anal and rectal mucosa with oedema blurring the pectinate line Gently parting the buttocks resulted in reflex anal dilatation by approximately a further centimeter. There were no abnormal neurological signs. Careful questioning of both parents independently yielded the same story: the anus had become patulous on the previous day, from which time his diarrhoea had been 'running out of him'

During his admission he developed the colitis associated haemolytic uraemic syndrome No pathogens or toxins were isolated from his stools, although it is thought that most patients with this form of the disease have been infected with verotoxin-producing *Escherichia coli* Six weeks later his anus was entirely normal, and remained so on a subsequent admission

We conclude that rectal inflammation may be associated with unexpected dilatation of the anus and the anal dilatation reflex It would be pertinent to ask 'how little (or how much) inflammation or irritation is required?' and, 'for how long after the inflammation has clinically settled can these signs persist?'

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Immunisation in the immunosuppressed child

Sir,

We read with interest the annotation on immunisation in immunosuppressed patients [1] The author highlighted the problems associated with viral infections and the need to determine immune state Chickenpox is a common infectious illness which can lead to major complications in immunosuppressed children. Unfortunately previous illness either before or during the period of immunosuppression does not necessarily confer protection. This is illustrated by two of our patients.

Case reports

Case 1. A boy, aged 3 years 5 months, first presented with a history of a progressive petechial rash. Physical examination showed pallor, bruising, and hepatosplenomegaly A bone marrow aspirate confirmed a diagnosis of acute lymphoblastic leukaemia. We were unable to obtain a history of chickenpox infection and viral titres were negative for varicella zoster virus He was started on chemotherapy. After 18 months of treatment he was admitted with shingles affecting the ophthalmic division of the right fifth cranial nerve He had a full course of acyclovir and recovered well. The titre for varicella zoster was less than 16 He was then restarted on maintenance chemotherapy but returned four months later with a severe illness associated with a typical chickenpox rash. He was again treated with acyclovir and at the end of this illness his varicella zoster titre had risen to 128.

Case 2. A 4 year old boy presented with a short history of bruising, pallor, and lethargy A diagnosis was made of acute lymphoblastic leukaemia. He had had a chickenpox illness during the first year of life and shingles six weeks before the onset of his acute leukaemia. Physical examination showed scarring in the right lumbar region consistent with shingles. Varicella zoster titre was negative He was started on chemotherapy but had a relapse of his leukaemia two and a half years later At this time his varicella zoster titre was 1 in 16. He was restarted on chemotherapy and three months later developed chickenpox with a typical rash which was managed successfully with acyclovir. He developed another mild bout of chickenpox two and a half years later, six months after completing chemotherapy.

These two patients illustrate the problems associated with varicella zoster infections and the difficulty in assessing immune state. It is therefore necessary to be vigilant and protect immunosuppressed chickenpox contacts with zoster immunoglobulin even in the presence of a history of exposure.

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The highly talented child

Sir,

I was most interested to read the article by Dr Lask, but wish to take issue with him on one point In the first paragraph he comments 'a 12 year old studying for an honours degree at Oxford University is clearly misplaced.' I fear that Dr Lask is falling into the trap of confusing gifted and highly gifted children I agree that, if a child has an IQ of 'only' 140 or 150, she would be misplaced at such an institution at such an age. Many researchers have found, however, that the highly gifted, that is with an IQ of 170 and over, are peculiarly handicapped in the true meaning of the word. they have learning and social difficulties and are children with special educational needs.

In a famous experiment at Harvard, several children with exceptionally high IQs were admitted as young as 12, and in the report following their graduation the principal, Professor Eliot, stated that these students had shown fewer psychological problems, been happier, studied better and more effectively, and shown just as good results in their examinations as the ordinary students. He felt that the experiment had been a great success

In the Stanford University's Longitudinal Studies of Giftedness, it was clear that if a gifted child was allowed full freedom to progress at his or her own rate he or she achieved their full potential and there were no psychological 'hang-ups' to sort out later It has also become clear that, contrary to popular misconception, the highly gifted do not burn themselves out early, but continue to show superior mental powers right through into old age—as, indeed, one would expect.

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Conductive education for motor disorders

Sir,

As a research orientated physician and the father of a baby with cerebral palsy I would like to comment on the recent controversy about conductive education, which you have recently highlighted in your journal [1, 2] Dr Beach suggests that the parents of children who are severely handicapped or who are making only slow progress are drawn towards such alternative forms of treatment' because of suggestions by 'family and friends, professionals, parents' groups, or by the media' [1] In some instances this may well be true, but I suspect that most parents do so, at least in part, because they have come to realise that their children's future is being compromised by the sad limitations of our health service Should parents really be expected to accept one or two hours physiotherapy per week (in some instances not even that) as being sufficient for their children? What would you do? No parent would dispute Dr Beach when he suggests that 'teams of dedicated professionals' look after their children [1] The rub is that there are simply not enough of them to go around! While there are justifiable doubts about the value of conductive education, I fear that there can be no doubt that the British system of care for children with cerebral palsy is grossly underfunded, and I cannot understand why the paediatricians and therapists who work in this field have put up with this for so long.

What then of conductive education? As a physician I suppose I should await the results of controlled clinical trials comparing this form of treatment with conventional treatment As a parent, however, I cannot afford to wait, and I have therefore asked for my child to be assessed at the Petö Institute If conductive education turns out to be of no benefit I will have lost comparatively little by taking him there On the other hand, if conductive education proves to be far superior to our conventional approach to treatment, I feel I will have enhanced my son's quality of life by taking him to Hungary The risk of not opting for conductive education at this time is, for me, too great to take.

I commend Mr Sutton and his colleagues at the Foundation for Conductive Education in their attempts to assess this form of treatment for motor disorders in a scientific way, and feel that this work is so important that it should be funded by central government and not left to the efforts of exasperated parents' groups and to charities While these studies go on it is also important that funds be made available to improve existing services for children with cerebral palsy, they deserve more than we currently provide for them

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Conductive education

Sir,

I have read with great interest the articles on conductive education [1] [2] It is widely accepted that there are variations in the availability of paediatric physiotherapy in this country and the methods of treatment No far sighted physiotherapist would be dismissive of progress in any child nor would wish to diminish parents' hopes without being unrealistic. It remains to be seen whether it is possible to transpose totally a philosophy from one culture to another

Mr Sutton ends his article with a quote from *Measure for Measure*· Claudio states 'The miserable hath no other medicine .' I add the Duke's reply,[3]

Happy thou art not;
For what thou hast, forget'st Thou are not certain

References

[1] Beach RC Conductive education for motor disorders new hope or false hope? *Arch Dis Child* 1988,63:211-3

[2] Sutton A Conduction education *Arch Dis Child* 1988,63: 214-7

[3] Shakespeare W. *Measure for Measure* Act III, scene 1

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Hyperkalaemia, cardiac arrhythmias, and cerebral lesions in high risk neonates

Sir,

The recent report by Shortland *et al* on the association between hyperkalaemia and cardiac arrhythmias in premature neonates is interesting but the proposed observations it reports are not substantiated [1] Bold statements about 'supraventricular tachycardia' and 'bradycardia' are unsupported and are contrary to experimental and previous clinical experience.

The authors have provided no evidence to support their diagnosis of 'supraventricular tachycardia ' They need to disprove an alternative interpretation that they were observing sinus tachycardia secondary to systemic hypotension and that intravenous calcium infusion raised the blood pressure, and only indirectly reduced the heart rate

All cases of supraventricular tachycardia have an identifiable underlying mechanism Although this can be detailed precisely by invasive electrophysiological study, it may also be predicted fairly accurately from a careful analysis of the electrocardiograms. Particular attention is paid to the atrial rate, the P wave morphology, the QRS morphology and the relationship between P waves and QRS complexes and valuable additional information may be obtained if the onset and termination of tachycardia are recorded The response to therapeutic manoeuvres may also provide an insight to the type of tachycardia. All episodes of bradycardia also have an identifiable mechanism. This may be slowing of sinus rhythm, or failure of sinus rhythm with a nodal or ventricular escape rhythm, or atrioventricular block. All of these have been reported in association with hyperkalaemia but bradycardias are also very common in sick premature neonates and are then of great independent significance.

The experimental and clinical effects of hyperkalaemia on cardiac rhythm are well described The raised serum potassium concentration reduces the resting transmembrane potential and thereby slows conduction Although 'excitability' may theoretically be increased, in practice this is not observed but, rather, automaticity is decreased as a result of depression of spontaneous diastolic depolarisation. Hyperkalaemia may produce a variety of arrhythmias and conduction disturbances. Those which have been described are varying degrees of atrioventricular block and interventricular conduction delay producing a type of bundle branch block. Supraventricular tachycardia has not been reported and would not be expected. The neonate with tachycardia reported by Cohen *et al* had an atrial rate of only 125/minute which was interpreted incorrectly as a tachycardia [2] In fact their patient showed sinus rhythm throughout with an interventricular conduction delay on one occasion and 2·1 atrioventricular block on another.

If we are to accept this report of supraventricular tachycardia caused by hyperkalaemia the authors should, therefore·

(1) Define 'supraventricular tachycardia' and 'bradycardia.'

(2) Detail the rate and the duration of tachycardia, and their relationship to plasma potassium concentration

(3) Describe the electrocardiographic characteristics of the tachycardias and the bradycardias. These may give a valuable insight into the mechanisms of the arrhythmias

(4) Provide information about any observed eletrocardiographic abnormalities which are known to occur in association with hyperkalaemia (such as T wave changes, QRS widening, prolongation and flattening of the P waves, etc)

It is important that the findings reported in this paper should be well substantiated because tachycardia secondary to hyperkalaemia in the neonate has not been reported previously Just as one would not consider a report on hyperkalaemia which did not define hyperkalaemia and give details of potassium concentrations recorded, so it is difficult to take seriously a report of 'supraventricular tachycardia' and bradycardia' which fails to define either arrhythmia and gives no details or documentary evidence

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[1] Shortland D, Trounce JQ, Levene MI Hyperkalaemia, cardiac arrhythmias, and cerebral lesion in high risk neonates *Arch Dis Child* 1987,**62:**1139–43

[2] Cohen HC, Rosen KM, Pick A. Disorders of impulse conduction and impulse formation caused by hyperkalaemia in man *Am Heart J* 1975,**89:**501–9

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Drs Shortland and Levene comment.

We read with interest the comments of Dr Wren We define supraventricular tachycardia as a heart rate of greater than 200 bpm with completely regular P waves on the cardiac monitor It is extremely difficult to perform full electrocardiography in a sick preterm infant and we do not have facilities for permanent paper recording In the infants that we have reported the cardiac rhythm converted over a matter of seconds from sinus rhythm to a supraventricular tachycardia and remained in that rhythm for some time before suddenly reverting to a slower rate This does not occur with sinus tachycardia due to systemic hypotension and we think that this is an unlikely cause for our findings We have defined a bradycardia induced by hyperkalaemia as a heart below 60 bpm lasting for more than 60 seconds in the absence of other clinically apparent causes (for example, hypoxia or endotracheal suction) The arrhythmias we have described all occurred when the serum potassium concentrations were raised, although in four infants the arrhythmia preceded the diagnosis of hyperkalaemia and in fact had led the medical staff to measure the serum electrolytes We are surprised that Dr Wren states that supraventricular tachycardia cannot occur during hyperkalaemia, although we agree that bradyarrhythmias are most commonly described. We encounter supraventricular tachycardia only rarely within the first 48 hours of life in the preterm infant but we have found that most occur at a time when the serum potassium concentrations are raised. Although the relationship between hyperkalaemia and supraventricular tachycardia is poorly described, we suggest that they are causally linked

Selective medical examinations on starting school

Sir,

We read with interest the article by O'Callaghan and Colver.[1] The authors describe a class review after the first term, but it is apparent that the children have already undergone a four to four and a half year check. From the review, 20% of children are selected to be seen, which may be a repetition of earlier work

It is not clear whether the four to four and a half year check is a population screen and whether the same doctor is responsible for the school review No data on the numbers of problems identified at this check are given, or whether any educational liaison is undertaken

In the Southampton area with a school age population of approximately 63 000 a selective system for school medicals has been in operation since 1970 All children are seen at six weeks and four and a half years, the latter representing a preschool medical examination usually performed by a clinical medical officer who is responsible for school follow up Problems from health visitor assessments at seven to nine months and two and a half years are selected for clinical medical officer attention Most defects are, therefore, identified *before* a child enters school.

The preschool examination permits an appraisal of the 'whole child' and all children seen are discussed with the headteacher and nurse. The doctor will select out those few children requiring school follow up Selection visits each term with the head/class teachers and school nurse follow, allowing continuity

The approach to selective screening adopted by the authors appeared to be rather disjointed involving a wide range of professionals We should like to be reassured that the doctor providing the service looks at the whole child and having done so, provides continuity from preschool to school years

In conclusion, the article gives the impression that selectivity is a new concept and suggests that blanket examinations are not necessary Two important factors seem to be missing—continuity of care and an appraisal of the 'whole child.'

Reference

[1] O'Callaghan EM, Colver AF Selective medical examinations on starting school *Arch Dis Child* 1987,**62**:1041–3

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Drs Colver and O'Callaghan comment:

Thank you for the opportunity to reply to the letter of Dr Berridge and colleagues. We are pleased that they also operate a 'selective system' and provide further arguments to support the concept.

We argued that 'selectivity' is an underused practice, not a revolutionary concept. A quarter of the children selected to be seen because the preschool record was not available had had their essential screening tests and to that extent there was repetition We do not understand the criticism that to gather information from people who already know the child is a 'disjointed' approach Technicians are trained to use the pure tone audiometer and the Keystone apparatus Altogether 98% of children were screened for hearing and vision, of whom 7% failed hearing and 4% vision Two children over the last five years received hearing aids after failing the hearing test and an unknown number received grommets We do not known the outcome of the vision failures but do know that 90% attended their family doctor or optician We recognised the gaps in information but already have clearer policy and more information than most health districts [1]

A different philosophy towards integration within primary care may distinguish the Southampton system from ours We feel that preschool surveillance should be integrated in primary care,[2] and that 'continuity of care' comes best from the family doctor who already provides continuity for the majority of medical problems. Parents and teachers are best placed to look at the 'whole child' in the first instance. If a concern presents through school which may have a medical component, we agree that the school doctor is then ideally placed to look at the whole child

The late Dr Tyrrell argued for fewer, better trained school doctors taking referrals from family doctors or school nurses, not duplicating their work.[3] Greater use of selective examination and greater emphasis on problem orientated work will help define this more restricted and difficult role.

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[2] Colver AF, Steiner H Health surveillance of preschool children *Br Med J* 1986,**293**:258–60

[3] Tyrrell S Community child health a big step forward *Lancet* 1984;**i**:725–7

Dry lung syndrome after oligohydramnios

Sir,

We were interested to read Professor McIntosh's recent paper describing 'functional' lung hypoplasia after preterm membrane rupture (PROM) [1] This has not been our experience among 30 pregnancies with PROM of greater than two weeks' duration followed prospectively; in that series some neonates developed anatomical but not 'functional' pulmonary hypoplasia (as defined by Professor McIntosh) [1] Eight of the 30 neonates died within 48 hours of life from respiratory failure, despite inflation pressures of up to 55 cm H_2O At necropsy pulmonary hypoplasia was confirmed in all [2] Of the 22 infants who survived, 11 required no respiratory support, and 11 required artificial ventilation One child had severe respiratory distress syndrome and required a maximum peak inspiratory pressure of 30 cm H_2O, but among the other 10 the mean maximum inflation pressure was 17 cm H_2O (range 12–25 cm H_2O)

Professor McIntosh attributed 'functional' lung hypoplasia to dry lungs, which resulted from leakage of lung fluid exacerbated by external compression on the fetal chest In our series lung hypoplasia occurred in pregnancies with membrane rupture at significantly earlier gestations than those pregnancies of neonates without pulmonary hypoplasia ($p<0{\cdot}01$). The degree and duration of the oligohydramnios produced by membrane rupture was, however, not significantly different between the two groups, which suggests that compression on the fetal chest cannot be the sole mechanism in producing pulmonary hypoplasia Indeed, the most significant difference between our two groups was the absence of fetal breathing movements in the group dying from pulmonary hypoplasia, confirming our preliminary findings reported earlier [3]

Our experience of a further five infants, ventilated during the same time period as our study group, but from pregnancies not complicated by PROM, has lead us to consider explanations other than a 'dry lung' for the ventilatory pattern described by Professor McIntosh [1] Three of the infants had severe respiratory distress syndrome, evidenced by classical chest radiographs, and two were septicaemic All five infants required high pressure ventilation (greater than 30 cm H_2O) both for resuscitation and subsequent ventilation After 72 hours, and with improvement in both conditions, the ventilatory pressures were rapidly decreased and all five infants were successfully weaned over the subsequent 48 hours.

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outcome in oligohydramnios due to membrane rupture in the second trimester. *Lancet* 1987,ii:129–31

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Marfan's syndrome in mitral valve disease

Sir,

We read with interest the report by Marlow *et al* on an infant with Marfan's syndrome and mitral valve dysfunction who died after acute illness with gross cardiac failure.[1] The authors stated that 'disease affecting the mitral valve is usually more benign than that of the aortic valve . . .'

This statement, however, may not be applicable to infants and young children with Marfan's syndrome. We have recently reported on the clinical course and the echocardiographic findings in 25 children with this syndrome.[2] Prolapse of the mitral valve leaflets was shown by echocardiography in all the patients and aortic pathology in 30% of the cases. Five patients died during the follow up period (mean 5±4·5 years), two of them were infants with severe mitral insufficiency and progressive congestive heart failure. The other three patients died during the second decade of life from complications of the aortic pathology. Another series reported by Sisk *et al* showed that among 15 patients with Marfan's syndrome diagnosed before 4 years of age, mitral valve dysfunction was the leading cause of cardiovascular morbidity and mortality.[3]

These data indicate that mitral valve disease is the most common cause of congestive heart failure and death in infants and young children with Marfan's syndrome.

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[3] Sisk HE, Zahka KG, Pyeritz RE. The Marfan's syndrome in early childhood: analysis of 15 patients at less than 4 years of age. *Am J Cardiol* 1983;52:353–8

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Medical staffing in paediatric departments in district general hospitals

Sir,

Dr Nelson is right.[1] At this hospital we have only two senior house officers, often with no previous paediatric experience, on a 1:2 rota, without any intermediate cover, to cover general and neonatal wards including labour ward resuscitation. We do not therefore have a 1:3 rota, nor a 'safety net'. Five years of local discussions have not altered this. What is needed is a united and forceful voice from the British Paediatric Association nationally, coupled with specific advice for consultant paediatricians on how to get past the embargoes on increasing junior staff.

Reference

[1] Nelson R. Medical staffing in paediatric departments in district general hospitals. *Arch Dis Child* 1988,63:96–7

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Maternal narcotic abuse and the newborn

Sir,

We were interested in the report by AlRoomi *et al* concerning maternal narcotic abuse and its effects on newborn infants.[1] Women on Merseyside smoke heroin rather than inject it and we would like to report aspects of our experience of 37 infants born to women who inhaled heroin.

(1) AlRoomi *et al* used phenobarbitone and chloral as first line drugs for the treatment of symptoms, but they make no comment on the effectiveness of these agents. In our series 15 (40%) babies also developed withdrawal signs but our initial experience with phenobarbitone by injection was disappointing. We subsequently tried oral chlorpromazine, which we stopped using because of its epileptogenic potential, although it was effective. We now consider that treatment with pure aqueous morphine sulphate (0·125 mg) given orally and as required is pharmacologically appropriate, have found it effective, and would recommend its use.

(2) In our series only eight (22%) children were subject to legal constraints, compared with 38% in AlRoomi's series. While this may simply reflect a different approach to social management, it may be that heroin abuse by inhalation has less disruptive effects on family life.

(3) We also found that these children were not brought to hospital for follow up appointments. We now consider that community based surveillance is more appropriate.

Reference

[1] AlRoomi LG, Davidson J, Evans TJ, Galea P, Howat R. Maternal narcotic abuse and the newborn. *Arch Dis Child* 1988,63:81–3

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Deadly vaccination

Sir,

All doctors treating children need to know about a recently published paperback which catalogues in some detail the hazards of vaccination.[1]

The gist of this alarming book is that vaccinations are dangerous and ineffective, and that safe alternatives are available Measles vaccine is said to carry a high risk of sequelae including meningitis and multiple sclerosis Tetanus vaccine is alleged to cause a 'severe compromising of the immune function.' Pertussis vaccine is proposed as a cause of the learning disability currently suffered by 15–20% of American schoolchildren, not to mention a range of other neurological disorders. BCG, diphtheria, rubella, typhoid, influenza, and mumps vaccine are apparently just as bad, causing diseases such as cancer, diabetes, and arthritis The hazards of all immunisation procedures are alleged to be compounded by their supposed ineffectiveness.

The solution, urges the author, is to avoid conventional vaccination procedures. Instead, parents are advised to improve nutrition and hygiene, promote exercise, use homoeopathic vaccination procedures (for example, against pertussis), use acupuncture, give zinc and vitamin supplements, and massage the spleen (50 times per minute for five minutes, twice daily, for a week at a time). By a deft use of quotations from medical, alternative, and antivivisectionist material, as well as authorities such as George Bernard Shaw, and bolstered heavily by vague pseudoscientific innuendo, the author marshalls his arguments Shortly after the book was published, the author declared that AIDS is not a new disease at all,[2] and is in fact the result of polio immunisation [3]

Most doctors will not wish to read or possess this book, but they ought to be aware of its existence as it is being read by parents, some of whom have found the propaganda compelling

References

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[3] Chaitow L I accuse Aids a legacy of polio vaccine *Journal of Alternative and Complementary Medicine* 1987,5(9) 23

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Archives of Disease in Childhood, 1988, **63**, 686–687

Book reviews

Language Development and Disorders. Edited by William Yule and Michael Rutter Pp 482 £28 00 hardback Blackwell Scientific Publications 1987 ISBN 0-632-01522-5

This major work on all aspects of speech and language disorders has been long awaited and much needed With 472 pages of text, and very full and up to date reference lists to each chapter, it will be essential to workers in many disciplines who have a special interest in language development and its problems—including those in psychology, speech therapy, paediatrics, and special education At £28 it is very good value (as I can conscientiously say having bought my own copy before receiving one for review)

There are 31 contributors to the 29 chapters. They cover the classification, prevalence, and causes of language disorders, the nature and mechanisms of language development from the prelinguistic stage, including its neurobiology and the effects of the environment; and the relation of language and psychiatric disorders Also included are the particular language problems associated with impaired vision, hearing, and intelligence: assessment, and intervention including the use of sign language and microcomputer technology

The style and standard of the chapters varies. The five to which Rutter contributes are predictably good, and models of clarity They state clearly some of the questions one is most often asked (for example, Do nurseries help? What sort of parental talk helps children's language most? What about bilingual homes?), review the evidence concisely and give the answer if there is one Other excellent chapters are those by Bishop and Rosenbloom (classification), Fletcher (language development), Freeman and Blockberger (deaf and blind children's language). Yule and Bax (assessment), and Kiernan (non-vocal communication systems)

The main fault of the book is that it is too long, if it is regarded as a book rather than a series of connected essays The dutiful reader who studies it from cover to cover will have forgotten the beginning before he reaches the end There is a lot of duplication. Specific developmental language disorders, the effect of glue ear and the Landau-Kleffner syndrome are among the many topics covered more than once Furthermore, the same evidence is sometimes used, without editorial comment, in different chapters to reach different conclusions. Concerning the effects of horrifically extreme deprivation, Puckering and Rutter review nine cases, and conclude that there is probably no critical period for language development in early childhood. In the next chapter, Goodman addresses the same issue, and referring to one of these cases ('Genie') reaches an opposite conclusion.

Then, on the question of whether the characteristic features of baby talk ('motherese') are important in helping normal children's language development, Wells and Gutfreund suggest they are, whereas Puckering and Rutter appear to dismiss their importance at one point, but then take a different view at another Again, on the prevalence and time course of language delay, Bishop and Rosenbloom say that the prevalence falls steeply between ages 3 and 5—which sounds reasonable However they cite Silva's Dunedin study as evidence for this It is therefore puzzling in Silva's own useful chapter to see a Venn diagram showing that in a sample of 857 children followed longitudinally, 37 had language delay at age 3, and 48 had it at 5 (though these only included 20 out of the 37 delayed at 3) The explanation must be that Silva's definitions were based on the 5th centile, so the number of children regarded as delayed at any age must be roughly the same

The editors could have omitted some chapters altogether, thus avoiding duplication, and they could profitably have added editorial footnotes explaining some of the apparent contradictions. Nevertheless, they and their contributors have produced an indispensable volume It is interesting to compare it with the much slimmer volume in the same series on *The child with delayed speech*. published in 1972, and to see the great increase both in interest and in knowledge of this topic over the past 15 years

R J ROBINSON

Road Accident Statistics. By T P Hutchinson Pp 292: £28 hardback Rumsby Scientific Publishing, 1987 (Available only from the publishers at PO Box 76, Rundle Mall, Adelaide, South Australia 5000.) ISBN 0-7316-0653-1.

From the slightly racy style of writing, with a free use of the first person singular, it would almost seem as if the author is hoping that this tome will be read from cover to cover It is, however, a compendium of information collected from all over the world on road traffic statistics, their methods of collection, their accuracy, and the differences between police and health statistics The author's obsession with every detail is to be commended in many ways, but for a paediatrician looking for simple information on the situation in the United Kingdom, it would be just as easy to find it in *Road Accidents Great Britain* published annually by the Department of Transport. This book is much more a source of information for specialists groups

R H JACKSON

Paediatric Hip Disorders. By G C Bennet. Pp 273· £44·50 hardback Blackwell Scientific Publications, 1987 ISBN 0-632-01509-8

This relatively slim volume covers the whole range of disorders of the hip in children There are 11 chapters and eight different contributors all from teaching centres in the United Kingdom, except for a solitary Australian, I P Torode from Melbourne. The editor contributes two chapters by himself After introductory sections on the development of the hip and the paediatric consultation, major problems such as congenital anomalies of the femur, congenital dislocation of the hip, the irritable hip, and the infected hip are discussed. The longest chapter in the book is a comprehensive account of congenital dislocation of the hip from infancy to adolescence by Martin McNicol of Edinburgh Perthe's disease is described by Anthony Catterall, who is an acclaimed authority on the subject He makes the point that in a disease in which 60% of patients do well without treatment it is important to have factors in prognosis to clearly define the 40% for whom treatment is required He advises operative containment of the femoral head at risk or for those children

resent late and have persistent pain
ia and tumours are included in the

rall the book is well presented with
illustrations and useful references. It
e read by orthopaedic surgeons in
ig and indeed by consultants who do
ive large children's practices All the
butors are orthopaedic surgeons and
e rounded picture could have been
ed if there had been one chapter by a
iatologist with paediatric expertise as
are a number of occasions where a
al opinion is invaluable Overall the
is to be congratulated

L KLENERMAN

Health Clinics. By Margaret Barker
nathan Ferner Pp 120 £9 50 paper-
John Wiley and Sons Ltd, 1988
0-471-91626-9

ook is designed as a simple intro-
n to the work of the child health
It is targeted at general practitioners,
l medical officers, and junior hospital
itricians It covers the general features
d health surveillance and the manage-
of the types of common physical,
, emotional, and behavioural prob-
hat present in the child health clinic
ile there is every virtue in being
, I feel that the book will leave the
to underestimate the level of clinical
nd knowledge that is required For
le, under the section of hearing
g, there is no emphasis on the level of
l training required to do this com-
tly Under hearing testing and the
f the nurse in the clinic, it says that
linic nurse can help with testing
ig, though again with no mention of
aining that would be needed
re are various other pieces of advice
which many of us would disagree For
le, the suggestion that all children
growth curve is persistently below
d centile should be referred. Another
le which many would disagree with
he statement that children with un-
ded testes should be referred by the
f 6 if possible
rall, this is a disappointing book It
detail and there are many statements
in it with which I would disagree, and many omissions of further information that I would regard as important The final chapters of the book covering child abuse and handicap I found much more helpful and provided a useful summary for the child health clinic doctor

L POLNAY

Developmental and Neonatal Hematology. (Pediatric Hematology/Oncology Series). Edited by James A Stockman III and Carl Pochedly Pp 348 $86·50 hardback Raven Press, 1988 ISBN 0-88167-339-7

This volume, written by a group of American authors, sets out to review current knowledge and document progress in the haematology of the fetus and neonate It does not aim to provide comprehensive coverage of all aspects of the field, and the book suffers like many other multiauthor reviews from some degree of duplication However, there are some excellent contributions within it

Several areas of current interest are well dealt with by one or more authors The chapters dealing with neonatal haemostasis and platelet function strike a good balance between the basic physiology and its clinical application Erythropoiesis by Mark S Brown is similarly well structured, with chapters on fetal and neonatal erythropoiesis, followed by chapters dealing with physiologic anaemia of infancy and factors influencing its severity

The review of blood component treatment points out clearly the risks of transfusion in the neonatal setting, and should be useful reading to anyone regularly involved in paediatric transfusion Another highlight is the very thorough chapter on neonatal isoimmune thrombocytopenia by V Blanchette It might, however, have benefitted from more discussion of the commoner problem of maternal and neonatal autoimmune thrombocytopenia somewhere in the volume.

On the negative side, the chapters on haemolytic disease of the newborn do have some duplication and one questions whether technical details of exchange transfusion techniques are appropriate in this setting.

Overall, this book achieves its purpose It provides several stimulating reviews in key topics, it is well written, very well referenced, and clearly indexed It will be useful to interested haematologists and paediatricians dealing with neonatal problems The excellent physiologic reviews, however, merit a wider readership

P J DARBYSHIRE

Adult and Pediatric Urology. Edited by J Y Gillenwater, J T Grayhack, S S Howards, and J W Duckett Pp 2095: £168 hardback (two volumes). Year Book Medical Publishers, 1987

This book gives a broad, up to date and very thorough review of urology from 91 authors. Despite its large size (two parts, 2095 pages and 7·3 kg) it is very readable. Each subject is comprehensively discussed, beginning with basic concepts and covering the relevant physiology, anatomy, and pathology as well as the detailed diagnosis and treatment

The bulk of the book is defined as covering adult urology, with just over one quarter being devoted to paediatric practice Much of the adult section, however, deals with general subjects that are highly relevant to paediatric urology These include chapters that give general background information such as the principles of the various diagnostic imaging techniques, and chapters covering conditions such as calculus formation and management, trauma, renovascular hypertension, and bladder dysfunction

Much of the paediatric section deals with congenital abnormalities and presents the different view points on the management of difficult problems, including the arguments for and against antenatal intervention for urological anomalies It also deals with current concepts of managing vesicoureteric reflux and covers aspects of transplantation in children

This book has drawn together a large amount of information and will be of value to paediatric surgeons and paediatric nephrologists and of interest to general paediatricians for occasional reference

M G COULTHARD

Archives of Disease in Childhood, 1988, **63,** 688–698

British Paediatric Association

Annual General Meeting, University of York, 12–15 April 1988

Abstracts for plenary spoken sessions

Molecular cloning and expression of a chlamydial genus-specific epitope. I Allan and ER Moxon (Oxford).

Chlamydia trachomatis is a major cause of sexually-transmitted disease and, as a consequence, poses a considerable threat of conjunctival and respiratory tract infection to the neonate. However, despite the medical and biological importance of chlamydiae, progress in the study of their pathogenesis, biology and antigenic composition has been limited by difficulties in culturing and purifying these fastidious parasites Therefore, adopting an alternative strategy, DNA was purified from *C trachomatis* (serovar L2), partially digested with restriction enzyme Bam HI, ligated into the plasmid vector pUC13 and a genomic library was constructed by transformation of *Escherichia coli* Bacterial colonies containing recombinant plasmids were subsequently screened with a monoclonal antibody which recognises an epitope shared by all members of the genus *Chlamydia* and which is located in the lipo-oligosaccharide present in the outer membrane of the parasite Six recombinant bacterial colonies which reacted positively with the monoclonal antibody were identified. All possessed a common Bam HI fragment of 6 9 kilobase pairs (kbp), with the transforming activity to produce monoclonal antibody reactivity being excised from 1·7 and 0·8 kbp PstI-Bam HI and Bam HI-EcoRI fragments lying within this stretch of DNA. Analysis of lipo-oligosaccharide from the recombinant *E coli* by polyacrylamide gel electrophoresis showed all six to possess a more rapidly migrating component which was reactive with the monoclonal antibody.

The cloning of this chlamydial component and the characterisation of the DNA and gene products encoded by it provides a potentially valuable tool for the study of the pathogenesis and also the diagnosis of this pathogen.

Normal placental transfer in the human. MD Bain, DK Copas, MJ Landon, and TE Stacey (Harrow and London).

Placental insufficiency, implying inadequate transfer functions, is frequently incriminated as contributing to perinatal morbidity and mortality Inadequate transfer of what, and by how much, is unclear.

We have measured placental transfer in normal human placentae at term, of four substances with molecular weight range 182–5000, namely, mannitol, lactulose, Cr EDTA and inulin This range covers many of the important fetal nutrients. A steady state maternal profile was achieved by a bolus and continuous infusion of a solution of these markers As they are inert, and solely and wholly excreted by the kidney, net placental transfer before delivery equals the total subsequent neonatal urinary excretion.

Placental transfer, expressed as a clearance, was derived by dividing the net transfer by the time-averaged transplacental concentration gradient. Clearance, K ml.min^{-1}, for mannitol was 7·3 (range 4·7–10, n=9), lactulose 6·6 (3·6–8·6, n=7), Cr EDTA 4·0 (2·6–5·2, n=5) and inulin 0·85 (0·63–1·26, n=9). These values indicate the placenta to be a significant barrier to transfer by passive diffusion, highlighting the necessity for carrier-borne transport mechanisms for substances such as glucose.

Growth in childhood and mortality in adult life. DJP Barker, CM Law, and C Osmond (Southampton).

There is increasing evidence that influences acting early in life are major risk factors for stroke, ischaemic heart disease and chronic bronchitis. Part of this evidence comes from epidemiological observations of striking geographical relations between current mortality from these diseases in England and Wales and indices of maternal and child health in the early years of this century. Relationships between adult diseases and childhood influences can be explored through height, since this is largely determined by growth in early childhood Using data from the three national birth cohorts we have shown that differences in average heights between the counties of England and Wales have persisted over 50 years. There is a strong inverse relation between average height in the counties and mortality from the three diseases The distribution of stroke also correlates with geographical differences in mean blood pressures of mothers and their 10 year old children There is a strong positive relation between height and cancer of the breast, ovary and prostate which suggests that promotion of child growth has disadvantages as well as benefits.

We have also analysed place of birth of two million people who died in Britain during 1969–72. The risk of dying from stroke, ischaemic heart disease and chronic bronchitis is related to place of birth within Britain, independently of subsequent migration. Differences in child growth may predict future differences in adult disease.

Adults born with oesophageal atresia and tracheo-oesophageal fistula. P Chetcuti, N Myers, S Beasley, and P Phelan (Melbourne, Australia).

One hundred and twenty five of 145 survivors born with oesophageal atresia and tracheo-oesophageal fistula prior to 1969 were reviewed to evaluate the outcome in an adult population. All case notes were studied, patients interviewed and examined and detailed lung function performed. The majority are comparable to their peers.

Over half had symptoms referrable to the upper gastrointestinal tract and a third complained of wheezing in the 12 months prior to review, but in the majority the symptoms were occasional Hospitalisation was required in only three patients, for pneumonia Lung function data showed evidence of mild obstructive airways disease with a mean % predicted forced expiratory volume in 1 second of 85·06.

The eventual outcome is encouraging. Knowledge of this will improve counselling of parents of children with the condition who often require frequent and prolonged hospital admissions after initial surgery.

When is a cluster a cluster? When it is next to a Nuclear Power Station?? AW Craft, S Openshaw, M Charlton, and J Birch (Newcastle upon Tyne and Manchester).

Unusual geographical and temporal aggregations of leukaemia have been described for over 60 years. Many techniques have been developed to determine whether clusters are anything other than chance but the matter is unresolved. Much recent work has centred on the nuclear industry and there have been several reports of clusters of leukaemia around such installations although most have started with this as an a priori hypothesis. A method has been developed to look dispassionately at a population independently of any preconceived ideas as to causation and disregarding arbitrary administrative boundaries. Registration data for 1968–85 from the Newcastle and Manchester children's cancer registries, a total population of almost 9 million, have been analysed. A series of overlapping circles measuring 1–25 km have been constructed which totally cover the whole of the study area with 812 993 circles. The rate of cancer for each circle is retrieved using postcoded registration data and 1981 census population information The significance of each circle is determined using a Monte Carlo simulation technique and circles surviving a level of $p<0\cdot002$ are drawn. If the distribution were Poisson then 173 circles would be expected to survive and be scattered all over the map. Wilms' tumour, which has been thought to be randomly distributed, fits this pattern. However, that for acute leukaemia, both myeloid and lymphoblastic (ALL) and non-Hodgkins lymphoma are not random and dramatic clusters appear on the map, most being nowhere near a nuclear installation. For ALL 1972 circles survive at $p<0\cdot002$. This technique will *define* a cluster When applied to data from the whole of the United Kingdom new insights will be provided into the aetiology of childhood cancer It can also be applied to any rare disease or conditon. Neural tube defects are currently being examined

Red cell membrane sodium (Na) transport in children—its possible genetic role and use in identifying the child at risk of essential hypertension (EH). JE Deal, V Shah, G Goodenough, and MJ Dillon (London).

Abnormal red cell membrane Na transport, manifested by high intracellular Na concentration (IcNa), low Na efflux rate constant (ERC) and decreased numbers of Na-K ATPase pump sites (Bmax) have been previously reported by us in children with EH It is unclear whether these abnormalities are caused by hypertension, are a cause of hypertension or are just markers for hypertension. Using the same methods 28 index hypertensive children and their families were studied. In 15 families one or both parents had EH or a strong positive family history of EH. In 13 families neither parent had EH nor had a positive family history. Significant differences were found between the children with a positive family history of EH compared with those without Mean (SD): IcNa (mMol/l cells) 8·19 (2·18): 6·41 (0·98) $p<0\cdot001$; ERC 0·4873 (0·1379): 0·5831 (0·1104) $p<0\cdot01$, BMax (nMol/l cells) 7·96 (1·71)· 9·56 (1·7) $p<0\cdot001$. There was a strong correlation between children and their parents in terms of IcNa, $r=0\cdot60$ $p<0\cdot001$; ERC $r=0\cdot51$, $p<0\cdot001$ and BMax $r=0\cdot42$, $p<0\cdot001$. No correlation was found between IcNa, ERC or BMax and age, body mass index, urinary Na excretion, plasma renin activity and systolic or diastolic blood pressure standard deviation scores.

Our data suggest that abnormal red cell membrane Na transport has a familial component and although not caused by the hypertension it may be the earliest pathophysiological step in its development, perhaps allowing the identification of children at risk of EH.

Improving prognosis for cystic fibrosis in the United Kingdom 1977–85. JA Dodge (on behalf of the BPA Working Party on Cystic Fibrosis).

This study attempted to identify all patients with cystic fibrosis alive in the United Kingdom at any time between 1977 and September 1985. A total of 6220 subjects were entered into the database. Age-specific mortality rates were calculated for the two periods.

Considerable improvement in prognosis has occurred during the period under study, particularly in the under 5 years age group. Comparative data also showed that survival is better in patients managed in large cystic fibrosis centres than in small local clinics.

Current survival: large v small clinics

Survival to age (years)	*Males*		*Females*	
	Large %	*Small* %	*Large* %	*Small* %
1	97·2	96·1	94·8	95·3
5	94·7	92·0	91·8	89·9
10	87·2	85·5	83·5	79·6
15	77·5	70·8	69·0	65·8
20	64·5	50·0	49·7	48·2
80%	14 years	11 years	12 years	10 years
50%	25 years	20 years	23 years	20 years
Age standardised mortality/1000/year	19·9	29·4	23·1	32·4

Regardless of any future improvements in treatment, numbers of adult patients with cystic fibrosis will inevitably increase in the United Kingdom during the next decade, highlighting the need for appropriate medical services.

Incidence of and risk factors for cerebral palsy in two national cohort studies. A Emond, J Golding, and G Peckham (Bristol and London).

It is widely assumed that the incidence of cerebral palsy has been reduced by improved perinatal care. This hypothesis has been tested using the 1958 British Perinatal Mortality Survey and the 1970 British Births Survey. In spite of a reduction in the stillbirth and neonatal mortality rates, the incidence of cerebral palsy remained constant at 2·5/1000 births. The prevalence at 10 years was higher in the 1970 cohort in which all children with cerebral palsy survived, whereas in the 1958 cohort 22% of cases of cerebral palsy (diagnosed between 1 month and 7 years of age) died before the age of 10.

A case control study, matching for mother's social class, age, parity and marital status, and the infant's sex, gestation and birthweight, was undertaken for all cases of cerebral palsy. (40 from 1958, 41 from 1970) Comparison of cases and controls showed no consistent differences with respect to social and environmental factors, history of pregnancy, labour or delivery Birth weight and gestation did not have a significant effect on the risk of cerebral palsy Major differences were apparent in the frequency of respiratory and neurological symptoms in the neonatal period.

These prospective data derived from two whole populations of births suggest that the majority of cases of cerebral palsy *are not* associated with an abnormal pregnancy, labour or delivery, and confirm that neonatal neurological symptoms are good predictors of subsequent cerebral palsy.

Parental smoking habits and wheezing and bronchitis in the child. JA Evans (Bristol).

Many authors have found associations between early bronchitis and/or wheezing episodes in the child and passive smoking, but few have attempted to ascertain at what age the child is most susceptible. Data to examine this were derived from the longitudinal study of the singleton children born to 17 000 women delivering in the United Kingdom during one week in April, 1970, who were followed up at the ages of 5 and 10. Smoking history of the mother was obtained in 1970, and for both parents in 1975 and 1980. Comparisons were made between children of four groups of mothers: those who smoked throughout pregnancy, those who gave up smoking during pregnancy, those who didn't smoke during pregnancy but whose parents smoked during the child's first 5 years, and households where neither parent smoked during the first 5 years of the child's life. After adjusting statistically for social and environmental factors associated with each aspect of smoking, wheezing and bronchitis in the child up to the ages of 5 and 10 years were both significantly more likely amongst the children of mothers who smoked during pregnancy. Apart from this, children whose mothers stopped smoking during pregnancy and those who were unexposed during pregnancy but exposed in the first 5 years did not differ in symptomatology from those whose parents were non-smokers throughout. The results would support a hypothesis of permanent damage to the fetal lungs due to smoking in the early stages of pregnancy.

Diagnosis of X linkage in sporadic cases of severe combined immune deficiency.

J Goodship, S Malcolm, Y Lung Lau, ME Pembrey, and R Levinsky (London).

Severe combined immunodeficiency (SCID) is a syndrome in which affected infants lack cellular and humoral immunity and die from overwhelming infection if bone marrow transplantation is not performed. With the exception of inherited deficiencies of adenosine deaminase and purine nucleoside phosphorylase the autosomal and X-linked forms cannot be distinguished clinically. Females carrying the X-linked form are immunologically normal.

The methylation pattern at the 5′ end of the PGK gene is different and constant between active and inactive X chromosomes In females heterozygous for the PGK polymorphism it is possible to distinguish between a population of cells with random X inactivation and a population with non-random X inactivation using methylation sensitive restriction endonucleases

We have previously shown that obligate carriers of X-linked SCID have a non-random population of T cells. We have now investigated women who have only one affected male child and where there is no previous family history of the disorder to see if they are carrying the X-linked form.

As the PGK gene is closely linked to the disease locus we can distinguish which polymorphic allele represents the inactive—that is, affected X chromosome—by its methylation. We therefore have a novel method of establishing linkage phase in women whom we show to be carriers without tracking alleles through the family. This is extremely useful when the woman may be a new mutation and she does not have surviving sons to establish phase It increases the number of women who can be offered early prenatal diagnosis.

Improved outcome following natural surfactant treatment in severe respiratory distress syndrome.

HL Halliday, G McClure, MMcC Reid, and B Robertson (on behalf of the Collaborative European Multicentre Study Group).

In a small randomised controlled trial of natural porcine surfactant (Curosurf) replacement in babies with severe respiratory distress syndrome (on mechanical ventilation, >60% oxygen, less than 15 hours old) we have shown a significant reduction in the complications of pneumothorax and intraventricular haemorrhage in treated babies. In an extended European Multicentre Study, mortality was also reduced (table).

	Treated (n77)	*Control (n69)*	*p Value*
Gestation (weeks)	28 8	28 4	NS
Birth weight (g)	1248	1333	NS
Oxygen need at entry (%)	80	80	NS
Mortality (%)	24 (31)	35 (51)	0 02
Pneumothorax (%)	14 (18)	24 (35)	0 05
Alive without BPD (%)	42 (55)	18 (26)	0 001

The 95% confidence limits for the reduction in mortality (4 to 36%) and survival without bronchopulmonary dysplasia (BDP) (18 to 40%) demonstrate a very important effect of this surfactant in the treatment of severe respiratory distress syndrome

In the eight collaborating European Centres surfactant is now administered to all babies with severe respiratory distress syndrome. Is it now unethical for all units not to treat these babies provided supplies of surfactant allow?

Mechanisms of transport of sodium and chloride and the effects of inflammation in the human infant colon.

HR Jenkins, V Schnackenberg, and PJ Milla (London).

A major function of the colon is the conservation of salt and water and we have previously shown that in the human infant it plays a major homoeostatic role.[1] Colitis may therefore assume greater importance especially in diarrhoeal diseases than in later life. The only previous studies of the mechanisms involved in infants have been in vivo where electrical gradients influence ionic movements. We have carried out a detailed study of transport in normal and inflamed isolated human infant colon using an Ussing Chamber and a voltage clamp procedure Stripped colonic mucosa normal (n=6 pairs) and inflamed (n=5 pairs) was mounted and bathed in Krebs solution. Under short-circuit conditions Na$^+$ (3·45 (1·53) µmol/hr/cm^2 mean (SD)) and Cl$^-$ (0·63 (3·61)) were absorbed and a residual ion flux consistent with HCO$_3^-$ secretion approximated Cl$^-$ absorption. Short circuit current (I^{sc}) (3·8 (0·28)) was very similar to net Na$^+$ movement and was markedly reduced by mucosal 10^{-4} amiloride (0·61 (0·7) p<0·01). Inflamed mucosa generated a lower potential difference (2·44 (0·1) *v* 6·5 (1·0) mV p<0·01) I^{sc} (1·62 (0·8) *v* 3·87 (0·5) p<0·02) and was of lower resistance (67·2 (12) *v* 104 (10) p<0·01). Na$^+$ was secreted and anion exchange reversed due to large increases of serosal to mucosal fluxes (Na$^+$

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[1] Jenkins HR, Fenton TR, Savage MO, Dillon MJ, Milla PJ Development of colonic transport processes in infancy *Gut* 1986;27:A1283–4

5·63 (0·1) to 15·7 (1·2) Cl^- 13·86 (1·64) to 20·9 (3) with no change in mucosa to serosal fluxes. These data show that Na^+ is absorbed electrogenically and Cl^- electroneutrally in exchange for HCO_3^-. In the presence of inflammation the electrical and flux changes suggest a decrease in resistance of shunt pathways which dissipate absorbed Na^+ and Cl^-. Inflammation of the infant colon therefore seriously impairs its ability to conserve salt and water, and would thus make an important contribution to a dehydrating diarrhoeal disease.

Acoustic emissions and automated BAER in the newborn. C Kennedy, P Evans, L Kimm, S Lenton, and R Thornton (Southampton).

Following presentation of an auditory stimulus via an ear probe, low intensity echoes from the cochlea—acoustic emissions—may be recorded by a receiver in the same probe and analysed using a programmable otoacoustic emissions measurement system (POEMS). In adults, acoustic emissions are always lost early in the course of hearing loss. In order to compare POEMS and ALGOTEK—an automated pass/fail test based on brain stem auditory evoked responses (BAER)—both tests are being used in addition to conventional BAER to screen newborns SCBU, other high-risk, and low-risk groups are being tested. All newborns who fail one of these tests and a random sample of those who pass are retested at 3 months of age and subsequently. In 70 newborns tested to date, acoustic emission was not recordable in one or both ears at or below 61 db in five, nor at or below 51 db in a further five. BAER were not recordable at or below 60 db in 1 nor at or below 45 db in a further five. Two newborns have failed on ALGOTEK. Further results including follow up data will be presented. Our results to date suggest a false-positive rate at 60 db not exceeding 7% for any of these three tests. Validation of ALGOTEK as a detector of auditory impairment is part of the present study However previous studies suggest that false-negatives for deafness do not occur with POEMS. POEMS requires only the insertion of an ear probe: no electrodes are needed and testing time is consequently short. POEMS may prove superior to currently available neonatal screening techniques for auditory impairment.

Electromagnetic stimulation of the motor cortex: a simple and painless technique to measure objectively corticospinal tract function in newborn babies and children. THHG Koh and JA Eyre (Newcastle upon Tyne).

Previously there has been no objective measure of corticospinal tract function in young children and newborn infants, resulting in the delayed diagnosis of cerebral palsy. Painless non-invasive electromagnetic stimulation of the motor cortex (EMSMC) is now possible; the latency from EMSMC to the evoked muscle action potential (MAP) has been shown to be a sensitive measure of corticospinal tract function in adults.

Following an assessment of its safety in an animal model, we have used EMSMC to study the maturation of the corticospinal tract and to assess its sensitivity to detect upper motor neuron lesions (UMNL) in children. One hundred and forty two normal subects (32 weeks' gestation to 50 years), 17 children with UMNLs (12 months–12 years) and seven comatose children with an acute encephalopathy (4–16 years) at risk of sustaining an UMNL were studied.

For EMSMC a pulsed magnetic field $\leqslant 1·9$ Tesla was used and MAPs recorded from abductor digiti minimi. For each subject the ratio, height (m)/latency from EMSMC to MAP(s), an index of conduction velocity (V_I) in the corticospinal tract was calculated.

MAPs were evoked in all the normal subjects including preterm infants, V_I increased with age from 10·5 m/s at 32 weeks' gestation until adult values (79 m/s) were achieved at 10–14 years. Ten of the 17 children with UMNLs had hemiplegia: on the affected side MAPs were absent in eight and abnormal in two; MAPs were all normal on the unaffected side. In the seven with bilateral UMNLs, MAPs were bilaterally absent in five, unilaterally absent in two. In the seven comatose children: all three with bilaterally absent MAPs died, two with unilaterally absent MAPs survived with hemiplegia on that side and two with bilaterally normal MAPs survived without handicap.

In conclusion EMSMC is a simple painless technique to assess the maturity and integrity of corticospinal tract function in young children We are currently assessing its potential for the early detection of cerebral palsy in a prospective study.

We thank the MRC and Newcastle Health Authority.

Antenatal diagnosis of fetal malformation—a population study. MJ Lewins (Hull).

To assess the success of a routine screening programme for structural fetal abnormality and to review the management of identified cases, all pregnancies within the population of Hull and East Yorkshire ending in 1986 were studied. From a total population of 500 000, 8232 pregnancies were included: 811 pregnancies ended spontaneously in the first trimester; 795 medical terminations of pregnancy were carried out; there were 34 stillbirths and 6592 live births

Major structural fetal abnormality was ultimately found to be present in 87 pregnancies, 40 of which were diagnosed antenatally Details of the type of abnormality, methods of diagnosis and management of the affected fetus and newborn will be presented.

Of the 795 medical terminations of pregnancy performed 22 were for identified fetal abnormality. All but one of these were for fetuses with either neural tube defects or major chromosomal abnormalities. In cases where a malformed fetus was identified and pregnancy continued a multidisciplinary counselling service was offered.

It was concluded that: (1) current methods of routine antenatal diagnosis identified less than 50% of major structural fetal abnormalities, (2) few fetuses with surgically correctable malformations were aborted; (3) the scope for antenatal counselling of parents of malformed children is limited but nevertheless potentially important.

Alteration in a calmodulin binding protein in cystic fibrosis exocrine glands. MA McPherson, RL Dormer, DK Shori, NA Bradbury, and MC Goodchild (Cardiff).

Although DNA probes closely linked to the cystic fibrosis locus have been discovered, the biochemical basis of the disease is unknown Cystic fibrosis is characterised by disturbances in mucus secretion and electrolyte transport in epithelial cells. Our studies showing defective β-adrenergic regulation of secretion of mucins and amylase in cystic fibrosis submandibular tissues suggested alteration in a regulator protein beyond the site of cyclic AMP formation.

While investigating this hypothesis, data suggested alteration in biological activity of the regulator protein calmodulin, which mediates the actions of Ca^{2+} in cells. This was not due to altered amount of structure of calmodulin itself

This change in activity of calmodulin was shown to correlate with alteration in a specific 61 000 molecular weight calmodulin-binding protein which showed a 21·6±6·0 (n=8 glands) fold increase in intensity of ^{125}I-calmodulin binding in boiled cystic fibrosis extracts compared with control (n=3 glands).

Such an alteration in a protein which modulates the actions of calmodulin could explain (a) defective protein secretion and electrolyte transport in response to β-adrenergic stimultion and (b) widespread disturbances in Ca^{2+} homoeostasis seen in cystic fibrosis and thus might be related to the genetic defect.

Placental potassium transfer. T Mohammed, C Sibley, J Stulc, and M Maresh (Manchester).

Fetal potassium accretion rates are high and in the rat, the placenta may protect the fetus from maternal hypokalaemia.[1] In humans fetal plasma potassium concentrations are reported to be higher than maternal at term.[2]

Potassium transfer was measured directly in the near term rat using placental perfusion. Following injection of radioactive potassium (K) or rubidium (Rb) Maternofetal clearance cl^{k}_{mf} or $cl^{Rb}_{mf}=(v \cdot Q)/A$ was measured after allowing time for a steady state to be achieved (v=venous perfusate and A=maternal plasma radioactivity, Q=flow rate) Fetoplacental (taken as a measure of fetomaternal) clearance cl^{k}_{fp} was measured for potassium from the steady state extraction of isotope added to the perfusate. Cl^{k}_{mf} was significantly higher than cl^{Rb}_{mf} (158±13 *v* 82±8 $\mu l.min^{-1}$ gram placenta^{-1}, $p<0{\cdot}01$). These values are both 10 to 20 times higher than would be expected for diffusional-transport via a paracellular 'pore' pathway.[3] Cl^{k}_{fp} was 124±13 $\mu l.min^{-1}g$ placenta^{-1} and calculated net materno fetal flux was 0·11 $\mu mol.min^{-1}$ g placenta^{-1}

Human cord ($[K_f]$) and maternal ($[K_m]$) plasma potassium concentrations were measured at elective caesarean section taking particular care to avoid hypoxia and haemolysis Samples were taken from the cord immediately after the baby was delivered with placenta in situ and on three timed subsequent occasions after delivery of the placenta $[K_f]$ at 5, 10, 20, and 30 minutes after laparotomy was 4·75±·15, 5·95±·26, 6·81±·23 and 7·59±·81 mmol kg. plasma water^{-1}. [Km] was unchanged following laparotomy (4·30±·13 & 4·26±·23).

We conclude that there is active transport of potassium across the rat placenta. In the human the previously reported steady state maternofetal concentration difference at term is unlikely to be present. It is not yet clear whether $[K^m]$ and $[K^f]$ are similar because they are closely controlled or because human placental potassium transfer is mainly passive.

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[1] Dancis JC, Springer D *Pediatr Res* 1970,4:345
[2] Faber J, Thornberg KL *Placenta* 1981,(Suppl 2) 203
[3] Robinson N, *et al*, *Placenta* 1987 (in press)

Acute retinopathy of prematurity: risk factors. YK Ng, AR Fielder, DE Shaw, and MI Levene (Leicester)

In a prospective study of retinopathy of prematurity (ROP) in infants of ≤1700 g birth weight, neonatal and ophthalmic data were obtained on 437 infants (including 19 heavier twin siblings). 220 infants (50·3%) developed acute ROP and the maximum severity was stage 1 in 130 infants, stage 2 in 63, and stage 3 or 4 in 24 (one had stage 4). Notable significant variables (p=<0·0001) relating to stage 3 and 4 ROP were: lower birth weight and gestational age, longer duration of assisted ventilation and time spent in increased oxygen, more apnoeas and bradycardias which required action including those for which oxygen was necessary, respiratory distress syndrome, a persistent ductus arteriosus requiring treatment, positive blood cultures longer duration of phototherapy, anaemia, and cranial ultrasound findings of haemorrhage The occurrence of pneumothorax, and cranial ultrasound appearance consistent with periventricular leukomalacia were also significantly related to acute ROP ($p<0·01$)

In the infants in whom blood gases were monitored only an arterial oxygen tension (PaO_2) >15 kPa in the first two weeks was marginally significantly related ($p=0·03$) to the stage of ROP which developed. There was a highly significant relation ($p=0·007$) between PCO_2 >13 kPa and acute ROP, and similarly with pH<7·2 ($p=0·002$) and base deficit of −8 or more ($p=0·004$).

These results support the suggestion that the pathogenesis of ROP is multifactorial

Heart and heart-lung transplantation in children: experimental or therapeutic? R Radley-Smith and M Yacoub (Harefield).

Since August 1984, 58 children under 15 years have undergone transplantation. Twenty seven patients aged 9 days to 14 years (mean 8·5) underwent heart transplantation. The main indications were dilated cardiomyopathy in 15 and congenital heart disease (CHD) in five Thirty one patients aged 10 weeks to 14 years (mean 8·4) underwent heart-lung transplantation (HLT) for pulmonary vascular disease—primary in five and secondary to CHD in 16. Four patients had parenchymal lung disease. There were seven (26%) and 10 (32%) early deaths: moderate pulmonary hypertension in the recipient and bleeding from previous thoracotomy were significant risk factors in each group respectively. With a mean follow up of 20·2 and 13·6 months, there were one and two late deaths in each group. Postoperatively patients were maintained on cyclosporin and azathioprine. Routine steroids were not given. All patients are well, growing normally and attending ordinary schools. One patient developed lymphoproliferative disease which has regressed completely Two patients after HLT developed obliterative bronchiolitis at 12 and 24 months, one patient required retransplantation. Routine annual reinvestigation has shown no evidence of chronic rejection in either group.

It is concluded that transplantation offers a chance of dramatic improvement in children with end-stage heart and lung disease, but long term function, particularly of the lungs, continues to need evaluation.

Infusion of T_3 restores the capacity of the pulmonary epithelium to reabsorb lung liquid in the hypothyroid fetal sheep. PM Barker, CA Ramsden, DV Walters, and LB Strang (London).

Lung liquid secreted by the fetal pulmonary epithelium needs to be reabsorbed from the alveolar space around the time of birth in preparation for air breathing. The capacity of the pulmonary epithelium to reabsorb this liquid depends on maturation of a sodium transport system which becomes increasingly sensitive to adrenaline towards the end of gestation

Hypothyroidism resulting from thyroidectomy at 113–120 days' gestation (term=147 days) in 12 fetal sheep significantly impaired maturation of the reabsorptive response to intravenous infusion of adrenaline (0·5 µg/minute). When dibutyryl cAMP was added to lung liquid, effectively bypassing the β-receptor, the reabsorption characteristics were not restored, suggesting that hypothyroidism has its effect elsewhere in the sodium transport system

The reabsorptive response to adrenaline was seen to develop normally in two fetuses thyroidectomised at 118 days in which a constant infusion of triiodothyronine (T_3) (120 µg/day) was given from 125 (fetus A) and 126 (fetus B) days gestation

Mean (SEM) lung liquid secretion (+) or reabsorption (−) rates before and during adrenaline infusion in control and thyroidectomised (T_x) fetuses of 135 days' gestation and over

	n	*Mean gestational age (days)*	*Before adrenaline (ml/hour)*	*After adrenaline (ml/hour)*
Control	15	137·7	+15·2 (1·5)	−11·5 (2·8)
T_x	13	139·7	+12·4 (1·3)	+5·2 (1·9)
In T_3 infused fetuses the results were				
Fetus A (T_x+10 days T_3 infusion)			+21·4	−4·0
Fetus B (T_x+10 days T_3 infusion)			+22·1	−9·0

The triple X girl. SG Ratcliffe and G Butler (Edinburgh).

Sixteen girls with the triple X chromosome abnormality were identified at birth by cytogenetic screening of 34 380 consecutive liveborn infants and are participating in a longitudinal study together with controls from the same population

The triple X girls had smaller head circumferences at birth and throughout childhood, presumably a reflection of slower brain growth Febrile convulsions occurred in 37% compared with 5% of controls There was a significant lowering of IQ scores (verbal 88, performance 95, full scale 91), speech therapy was required by 50% and educational intervention by 80% (compared with 12% of controls). Behaviour in school, assessed by the Bristol Social Adjustment Guide, showed appreciable under-reaction.

Sexual development was delayed in onset by approximately 1½ years and one girl developed secondary amenorrhoea associated with a unilateral streak ovary

The incidence of 1 in 1000 in the female population indicates that there will be around 25 000 triple X females in the United Kingdom yet the diagnosis is rarely made by paediatricians. Reports in the literature describe 16% of the offspring of triple X women to be chromosomally abnormal but this is likely to include biased reporting, and requires confirmation by continued study of population ascertained cases

Consequences of HIV infection in pregnancy: results from the European Collaborative Study. Y Senturia (on behalf of the European Collaborative Study).

Since the end of 1985, there have been 351 HIV positive laboratory reports to CDSC on adult women in England and Wales; 57% reported between January and September 1987. This increase is likely to be paralleled by an increase in paediatric infection. Although the outlook for children with AIDS is poor, little is known about the outcome for the much larger proportion of HIV infected children who have less severe or asymptomatic infection.

European centres are collaborating in a prospective study to determine the prevalence of HIV infection in infants born to positive mothers, to examine risk factors for vertical transmission (such as maternal clinical status, breast feeding and mode of delivery), to establish the natural history of HIV infection in childhood and to identify precursors of AIDS/ARC onset in infected infants.

One hundred and fifty six children from six centres had been enrolled by 8 December 1987 Mothers of all children were known to be HIV positive at or before birth; 10% had ARC/AIDS prior to delivery. Ninety seven of the 156 children had been followed for at least six months and 70 for over one year Eight had developed ARC/AIDS, five other children had substantial signs or symptoms, and 143 were clinically normal when last seen. Seventeen are known to be infected as assessed by virus culture, antigen test or persistence of antibody in the past 15 months: this is 20% of those whose infection status is known The situation in March 1988, when 83 children will have reached the age of 15 months will be presented.

Should paediatricians be more involved in the care of children with the most common cause of death and acquired handicap? PM Sharples, A Storey, A Aynsley-Green, and JA Eyre.

Head injury is the most common cause of death and acquired handicap in children yet there has not been a detailed analysis of the management and outcome of such children by place or by person. We have performed a region wide study of all children admitted with or who died from a head injury between 1979–1986.

Children admitted with head injury to 53 hospitals in the Northern Region were identified from the Hospital Activity Analysis; the data concerning deaths were obtained from the death certificates supplied by the Office of Population Censuses and Surveys, the coroners' reports and the hospital records

Altogether 25 009 such children were admitted to hospital for a total of 49 195 bed days, thus, one child in every 200 is admitted with a head injury each year. There was an equal distribution of children across all ages. Forty eight per cent were admitted without being under the direct care of a neurosurgeon or paediatrician. Six hundred and three (2·4%) were transferred from a district general hospital to the Regional Neurosurgical Centres (RNSC).

Two hundred and fifty four (1%) died, 63% of whom were boys; 160 (63%) were >8 years old. Thirty three (13%) died at the roadside and a further 106 (42%) were dead on arrival to hospital; 116 (45%) died after admission, 83 (72%) at a RNSC and 33 (28%) at a district general hospital. Only 20% of those who died at the RNSC were under paediatric care and 74% under neurosurgeons and anaesthetists. Seventeen per cent of those who died at a district general hospital were admitted under paediatricians, the remainder were admitted under adult general or orthopaedic surgeons. The majority of those who died at a district general hospital survived more than six hours and could have been transferred to a specialist unit. At least 25% of all children who died had potentially preventable causes of death.

Disquieting facts are revealed by these data. Further detailed analysis of the management of these children is being performed to define the services and the facilities that should be provided for optimal care both at the roadside and in hospitals

We thank Action Research and Newcastle Health Authority

Jejunal epithelial transport in cystic fibrosis. CJ Taylor, J Hardcastle, P Hardcastle, and P Baxter (Sheffield)

Cystic fibrosis is characterised by a defect in chloride transport in sweat duct and respiratory epithelial cells. We have recently demonstrated a similar defect in electrically monitored chloride secretion in gut epithelium, using a modified Ussing chamber technique. Jejunal biopsy samples from children with cystic fibrosis failed to respond when challenged with the intestinal secretagogues acetylcholine (ACh) and prostaglandin E (PGE_2), while control tissue exhibited a rise in potential difference (pd) and short circuit current (SCC) in response to these agents.

Further studies have been performed on biopsies from six children with cystic fibrosis (mean age 6·8 years) and six controls (mean age 4·9 years) using both 5 hydroxytryptamine (5HT) and agents acting intracellularly (dibutyryl cyclic AMP [dB cAMP] and the calcium ionophore A23187) Control tissue responded to all these secretagogues with an increase in pd and SCC. No response was obtained in cystic fibrosis biopsies to either the receptor mediated agents or dB cAMP although an increase in pd and SCC was observed with mucosal sodium linked glucose absorption Four cystic fibrosis tissues also responded to A23187 with an increase in SCC. Failure to respond to this wider range of secretagogues suggests that the defect in cystic fibrosis is at a common intracellular point that mediates secretion, beyond the generation of cAMP The response to A23187 would indicate that there is a failure to elevate or release ionised intracellular calcium.

***Campylobacter pylori* gastritis can be diagnosed serologically?** JE Thomas, EJ Eastham, TSJ Elliott, D Berkely, and D Jones (Newcastle upon Tyne and Manchester).

The aim of this study was to investigate the usefulness of anti *Campylobacter pylori* (Cp) antibody titres in relation to endoscopically proven active chronic gastritis in children aged 5–16 years.

Antral biopsies were obtained from 51 consecutively endoscoped patients and examined by culture, histology and scanning electron microscopy. Specific IgG antibodies to Cp were measured using a sensitive ELISA assay. Aged matched controls were obtained from a hospital based population with no significant gastrointestinal symptoms

The endoscopic results confirm the presence of Cp in 21% of patients and a strong association with active chronic gastritis All patients with Cp had circulating specific IgG antibodies, with positive titres of >1:1600. Their presence was 100% sensitive and specific In the control group only two of 51 patients (3·9%) had positive titres, in each case not exceeding 1:1,600 We conclude that Cp associated gastritis is associated with high circulating levels of specific IgG antibody and that their measurement is a useful investigation in children with upper gastrointestinal symptomatology.

Systemic *Haemophilus influenzae* type b disease in children in the Oxford region: implications of current conjugate vaccine trials. G Tudor-Williams, J Frankland, D Isaacs, RT Mayon-White, JA Macfarlane, MPE Slack, E Anderson, P Crook, and ER Moxon (Oxford).

Since January 1985 a prospective study of invasive *Haemophilus influenzae* disease in children in the Oxford region has been in progress. One hundred and fifty one cases of the type b (Hib) infection have been identified in the first 2¾ years of the study. Ninety six per cent occurred in children <5 years, 70% <2 years and 10% <6 months. Meningitis accounted for 67%, epiglottitis 11%, cellulitis 8%; pneumonia, joint infections or bacteraemia amounted to 14% In an estimated population 169 300 children aged <5 years, the cumulative risks of invasive infection and meningitis respectively are 1:645 and 1:950 children. There were four early deaths all in children aged over 6 months.

Hib capsular polysaccharide (PRP) has been shown to be poorly immunogenic under 2 years of age. Conjugation of PRP with protein enhances its immunogenicity in infancy. Several candidate vaccines have been produced, and the first efficacy trial of one such conjugate (PRP-D) in Finland has demonstrated an 87% protective efficacy (95% confidence interval=50–96%) in children immunised under 6 months. We are conducting a safety and immunogenicity study of a more highly characterised conjugate (capsular oligosaccharide covalently linked to a mutant diphtheria toxin, the HbO-C vaccine), two doses of which have been shown to stimulate significantly higher concentrations of antibody than three doses of PRP-D.

Ninety five per cent of this region's children receive at least two doses of DPT and polio, assuming a 90% efficacy for the HbO-C vaccine, incorporation of this into the primary immunisation schedule has the potential for preventing 42 cases of invasive Hib disease annually in the Oxford region.

The outcome for infants of less than 28 weeks' gestation. AM Weindling and RWI Cooke (Liverpool).

Offering intensive care to infants of <28 weeks is often questioned because of the possibility that the proportion of handicapped children may be increasing.

We have examined the outcome of 477 infants of 28 weeks and less born between 1980–1985 from Merseyside and North Wales and nursed at this hospital. Two hundred and fifty five survived. Seven were lost to regular follow up. All the others were assessed annually by general physical and neurological examinations with developmental screening Impairment was defined as moderate to severe developmental delay, cerebral palsy of any degree, or hearing or visual impairment sufficient to compromise developmental progress.

Three hundred and seven infants were born at <28 weeks' gestation and 126 (41%) survived. This compared with 170 infants born at 28 weeks with 122 (72%) survivors. Survival over this six year period improved slightly from 38% to 44% for infants <28 weeks and from 60% to 70% for infants of 28 weeks.

There was a gradual and steady decline in the proportion of disabled survivors. In 1980, 38% of surviving infants <28 weeks and 27% of 28 weeks survivors were disabled In 1985 the comparable proportions were 20% (<28 weeks) and 11% (28 weeks). The number of disabled infants expressed as a percentage of total births also declined from 15% in 1980 to 8% in 1985.

No infants of 23 weeks' gestation or less survived, although 3/31 infants of 24 weeks survived, all without disabilities.

The predictive value of somatosensory evoked potentials in the preterm infant. CP White, VJ Klimach, and RWI Cooke (Liverpool).

Somatosensory evoked potentials (SEPs) provide information about the functional integrity of the sensory system. The anatomical proximity of the motor and sensory pathways means that damage to the sensory pathways, as reflected in abnormalities of the SEP; may also imply damage to the motor pathways. Thus SEPs may prove useful in the prediction of neurological handicap in this group of high-risk infants

Thirty infants with ultrasound abnormalities were tested in the neonatal period and their results compared with those of 'normal' infants of corresponding gestational age Many had abnormally long latencies or absent responses At 2 years of age these children have been assessed for the presence of cerebral palsy or developmental delay

Seventy seven per cent of those infants with abnormal SEPs have signs of cerebral palsy and a further two children have delayed development. Eighty three per cent of infants with normal SEPs have no neurological abnormalities, however two children with normal SEPs have developed spastic diplegias.

Thus SEPs provide another method of predicting neurological outcome in the preterm neonate.

The temporal pattern and natural history of asthma in childhood. S Zeidan, H Ali, MJ Danskin, and EN Hey (Newcastle upon Tyne).

All 2700 of the 7 year old children in North Tyneside were screened for wheeze in 1979 with a questionnaire followed by selective clinical assessment (including bronchial challenge): 98% of the families responded to the questionnaire and 9·3% of the surveyed children had had episodic wheeze in the previous 12 months The symptoms of all those who were followed responded to one or more of the drugs used in the management of asthma, but only 12% of the symptomatic children were known by the parents to be asthmatic prior to the survey, and only 27% had previously had consistent bronchodilator treatment.

When the same cohort of children were reassessed eight years later (92% of survey forms returned), a third of those had had symptoms at 7 were now asymptomatic, but 100 new cases of asthma were found amongst children who had had no recognisable symptoms (according to parental questionnaire) in 1979. The point prevalence of asthma in children at 15 was, therefore, only marginally less (8·6%) than it had been at 7

More seriously, only 58% of the children who first developed recognisable symptoms after 1979 had yet received symptomatic bronchodilator treatment by the time the second survey was conducted, and only 53% knew that their symptoms were due to asthma, The School Health Service needs to recognise that many children who are asymptomatic at 7 develop troublesome asthma in later childhood. Previous longitudinal, community based, surveys have failed to highlight this issue.

Asthma sitll remains underdiagnosed and undertreated.

Meningitis during the first year of life—a two year prospective study. J de Louvois, J Blackbourn, R Hurley, and DR Harvey (London).

During the period September 1985–August 1987, 653 consultant paediatricians in the United Kingdom and Eire cooperated in a prospective study by completing monthly questionnaire cards, and by providing subsequent clinical information. Additional information was collected from the microbiologists, the CDSC, and OPCS. Altogether 1973 cases of meningitis were reported; M/F ratio 1·3/1. Four hundred and nine occurred during the neonatal period of whom 289 were bacteriologically proven—1/4000 live births. Group B streptococci (GBS) (25%) and *E coli* (17%) were the commonest isolates. *H influenzae, Str pneumoniae* and *N meningitidis* accounted for 13% of cases and *L monocytogenes* for 5%. In 5% of neonates treatment was based on chloramphenicol, in 24% on gentamicin and in 14% on cefotaxime. The overall mortality among the newborn was 20% (ranging from 30% with enteric G -ve rods to 0% when listeria or viruses were isolated). Culture negative cases of meningitis had a 3% mortality. Among babies older than 28 days *Str pneumoniae* (12%), *H influenzae* (36%) and *N meningitidis* (34%) accounted for 82% of cases and *E coli* or GBS for 6%. Mortality among babies over one month of age was 5%. The incidence was lowest in the Yorkshire and SW Thames Regions and highest in Northern Ireland and the SE Thames Regions. This is the largest and most comprehensive study of neonatal and infantile meningitis in the British Isles and in due course it will allow data on long term morbidity to be collected.

Prevalence of hypoxaemia in children coming to adenotonsillectomy. VH van Someren, J Hibbert, JK Stothers, MC Kyme, and [illegible] Morrison (London).

Enlarged tonsils and adenoids are the major cause of upper airway obstruction in children. However, the prevalence of such obstruction has never been determined. The main aim of this study was to establish how many children with adenotonsillar hypertrophy suffer night-time hypoxaemia. We also wished to identify the clinical features of those who do.

So far 42 patients have been studied preoperatively. Oxygen saturation (SaO_2), chest movement and ECG were recorded overnight. Awake SaO_2, mean SaO_2 during sleep and dips in SaO_2 $\geq 10\%$ below baseline were noted. Nineteen controls have also been studied.

All controls had mean SaO_2 values above 92·0% and less than one obstructive episode per hour. Eleven patients had mean SaO_2 $\leq 92{\cdot}0\%$ and 10 had obstructive episodes. In nine patients restudied postoperatively all these abnormalities were abolished.

A close association was found between awake and mean asleep SaO_2: seven of 11 patients with awake SaO_2 $\leq 95\%$, but only four of 30 with awake SaO_2 $>95\%$ had a mean SaO_2 $\leq 92{\cdot}0\%$ ($p<0{\cdot}01$). Preliminary analysis in 27 patients shows that those who obstruct have significantly more airway, but not infective, symptoms than the remainder.

Thus children with adenotonsillar hypertrophy and night-time obstruction are common and can be identified in outpatients by their symptoms and SaO_2 whilst awake.

We thank the MRC for support.

Detection of pulmonary surfactant in amniotic fluid by polarised light microscopy. HW Clark, W Jacobson (Cambridge).

Jacobson *et al* (1988) have reported the detection of pulmonary surfactant in tracheal aspirates by polarised light microscopy. Could this technique be used to detect the presence of surfactant in samples of amniotic fluid at birth to assess the risk of development of respiratory distress syndrome?

Altogether 136 samples were examined. Of 61 samples from births, 11 were of 24–35 weeks' gestational age and 50 were of >36 weeks. Seventy five samples were collected by amniocentesis at 16 weeks.

The unprocessed fluid was examined microscopically in polarised light for evidence of birefringent particles. The 50 specimens from mature fetuses contained one main type of particle which was identical to that observed in tracheal aspirates. these were round (0·5–3 μm diameter), strongly birefringent, and showed a cross of polarisation indicating layers of phospholipid. They were soluble in a 2:1 (v/v) mixture of chloroform:methanol.

Of the 11 premature samples, seven showed these particles, but four showed either none or very few and these four infants developed respiratory distress syndrome. None of these characteristic particles was observed in the 75 samples from amniocenteses.

Some particles of vernix are large (8–12 μm diameter) with a cross of polarisation and easily distinguished from the particles of surfactant. There was a good correlation between the presence of surfactant particles and the percentage of phosphatidyl choline in the sample.

Polarised light microscopy may thus provide a simple test for surfactant in amniotic fluid which could be useful in the diagnosis of respiratory distress syndrome.

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ARCHIVES OF DISEASE IN CHILDHOOD

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Annotations

Inherited peroxisomal disorders involving the nervous system *Stephenson* 767

Clinical significance of IgG subclass deficiency *Morgan and Levinsky* 771

Original articles

Rising asthma admissions and self referral *Storr, Barrell, and Lenney* 774

Simplified oral pancreatic function test *Puntis, Berg, Buckley, et al* 780

Faecal chymotrypsin: a reliable index of exocrine pancreatic function *Brown, Sule, Williams, et al* 785

Congenital hypothyroidism: increased incidence in Asian families *Rosenthal, Addison, and Price* 790

Dietary variation in diabetics *Hackett, Court, McCowen, et al* 794

Mineral accretion in the human fetus *Ryan, Congdon, James, et al* 799

Cardiac anomalies in Williams-Beuren syndrome *Hallidie-Smith and Karas* 809

Antineutrophil cytoplasm antibody in crescentic glomerulonephritis *Walters, Savage, Dillon, et al* 814

Urinary infection and malformations of urinary tract *Ring and Zobel* 818

How parents and families cope with chronic renal failure *Reynolds, Garralda, Jameson, et al* 821

Comparison of temporary and permanent catheters for acute peritoneal dialysis *Wong and Geary* 827

Reflex anal dilatation associated with severe chronic constipation *Clayden* 832

Short reports

Vomiting and gastro-oesophageal reflux *Paton, Nanayakkhara, and Simpson* 837

Body segments and growth hormone *Bundak, Hindmarsh, and Brook* 839

Fatty liver and medium chain triglyceride (MCT) diet *Beverley and Arthur* 840

HIV infection in Zimbabwe *Topley* 842

Atypical presentation of subacute thyroiditis *Geva and Theodor* 845

Sweat tests and flucloxacillin *Williams, Griffiths, Green, et al* 847

Mineral content of rib bone in infant deaths *Ryan, Variend, James, et al* 848

Functional residual capacity related to hepatic disease *Greenough, Pool, Ball, et al* 850

Melatonin state in Mendenhall's syndrome *Rittey, Evans, Gray, et al* 852

Collodion babies with Gaucher's disease *Lui, Commens, Choong, et al* 854

Controversy

Preadmission antipyretics in Reye's syndrome *Hall, Plaster, Glasgow, et al* 857

Commentary *Mowat* 865

Current topic

Childhood causes of adult diseases *Barker* 867

Personal practice

Management of perinatal bereavement *Morris* 870

Correspondence 873

Book reviews 877

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Annotations

Inherited peroxisomal disorders involving the nervous system

For genetic reasons peroxisomes may be absent or lack one or more of their enzymes. The result may be subtle and long delayed, but is often catastrophic and immediately recognisable as a serious disorder at birth. The trouble for the clinician is that it is often not possible to make a diagnosis unless the right tests are thought of: these tests are not part of routine 'metabolic screens.' It is first necessary to frame the question 'could this be a peroxisomopathy?' The object of this annotation is to help with when and how to answer this question

Peroxisomes

Peroxisomes are subcellular organelles with a single membrane which occur in every cell apart from the mature erythrocyte. They are seen best by appropriate preparation of a biopsied liver specimen where they are about 0·5 μ in diameter and round on section. A high concentration is inferred in other tissues including proximal renal tubules, adrenal cortex, brown fat (particularly in cold adaptation), and myelin forming glia. Peroxisomes, in addition to the peroxidation from which the name derives, are involved in numerous metabolic processes. For clinical diagnostic purposes the most important enzymatic actions to be aware of are the β oxidation of very long chain fatty acids (VLCFA), the synthesis of bile acids, and the synthesis of ether glycerolipids (plasmalogens), the latter involving the enzyme acyl CoA:dihydroxyacetone phosphate acyl transferase which is commonly known as DHAP-AT. Although not conclusively proved at the time of writing, the location of the phytanic acid oxidase which is deficient in Refsum disease must also be in the peroxisome.

Classification of inherited peroxisomal disorders

Inherited peroxisomal disorders are classified into three groups. In group 1 are conditions in which peroxisomes are absent or greatly diminished, with a generalised impairment of peroxisomal functions In group 2 peroxisomes are present but there is an impairment of some but not all peroxisomal functions. In group 3 only a single peroxisomal function is defective. Because of the great importance of the peroxisomal enzymes involved in the β oxidation of VLCFA and the use of measurements of VLCFA in diagnosis, this group is itself subdivided. Group 3A includes those conditions in which VLCFA oxidation is impaired and thus VLCFA accumulates, and group 3B those in which the single enzyme defect is of another sort.

GENERALISED PEROXISOMAL DISORDERS (GROUP 1)

The now classical example is the cerebro-hepato-renal syndrome of Zellweger.[1] [2] The typical neonate is more dysmorphic than a baby with Down's syndrome with high forehead and huge fontanelle with metopic extension. Inactivity is even greater than in the Prader-Willi syndrome and hypotonia especially of the muscles of the neck is profound. Epileptic seizures commonly begin in the neonatal period. Because of general unresponsiveness it is difficult to tell that the infant is blind and deaf, but the electroretinogram (ERG) and brainstem auditory evoked responses (BAER) are both flat. The liver is firm and the renal cortex is echogenic. Calcification of the patellae and other cartilages may overshadow the considerable retardation of the bone age. Malformations of the heart or gut may be present and dominate the clinical picture. After early death, general pathology shows hepatic fibrosis, renal cysts, and small adrenals with striated inclusions (the striations representing VLCFA). The brain shows both malformation and degeneration. All the features of Zellweger syndrome appear to stem from a virtual lack of peroxisomes and their functions.

More difficult to recognise in group 1 are the milder variants of Zellweger syndrome. Complementation studies suggest that mild Zellweger syndrome, infantile Refsum disease, and hyperpipecolicacidaemia may be the same disorder.[3] Four recent publications include photographs of the faces of these children up to age 13 and the similarities are considerable[4–7] Characteristically the lobule of the ear is unformed and the palate high arched. Presentation may not be with neurological problems but rather with failure to thrive and steatorrhoea, and low plasma cholesterol and vitamin E concentrations. Clues to the peroxisomal aetiology come from the palpable liver, the retarded bone development, and the defects of vision (retinal) and hearing (sensorineural) which become apparent. Dots of pigment on the retina are characteristic. With time, development ceases and although these children may be mobile they show considerable mental handicap perhaps with autistic features. Originally some of these children were regarded as having a variant of Refsum disease (see below) but it is now clear that when there is a generalised peroxisomal deficiency phytanic acid from the diet accumulates with age.[8]

The last of the current members of group 1 goes by the title of neonatal adrenoleukodystrophy (NALD). It got this name because of its pathological resemblance to X linked adrenoleukodystrophy the first member of group 3A. Complementation studies indicate that it is genetically distinct from the others.[3] Affected infants may be hypotonic and have neonatal seizures but early disorder of development may be mild. Dysmorphic features are also slight—facial photographs are included in three recent reports.[9-11] Retinal blindness may be the over-riding early feature so that the infant is regarded as having Leber's amaurosis.[12] Later, neuropathy is common.[9 13] The most characteristic part of the history, however, is that after even a few years of progress there is regression, often abruptly after a febrile illness, with loss of skills and neurological functions and fatal outcome.

IMPAIRMENT OF SOME PEROXISOMAL FUNCTIONS (GROUP 2)

Rhizomelic chondrodysplasia punctata (RCDP) is the only certain disorder having a defect in a selected number of peroxisomal functions[14] but it may be that the Conradi-Hünermann form[15] will also become included. Infants with RCDP should be easily recognisable by the proximal shortening of their limbs and epiphyseal calcifications, cataracts, and (if survival is sufficiently long) evidence of mental handicap.

DEFECTS OF A SINGLE PEROXISOMAL ENZYME (GROUP 3)

Our knowledge of disorders of a single peroxisomal function (group 3) is expanding at a great rate. This is primarily so in group 3A which now contains four conditions having a primary defect in VLCFA metabolism. The identity of the respective enzyme deficiencies has been established in little over a year.

Disorders with accumulation of VLCFA (group 3A)

Adrenoleukodystrophy (ALD) presents in boys as either school failure due to central demyelination (visible on a computed tomogram) or as adrenal insufficiency, hence the old name Addison-Schilder disease. A remarkable feature of this X linked disorder is extreme variability within pedigrees,[16] so that later onset adrenomyeloneuropathy (presenting with spastic paraparesis) or adult onset ALD may coexist. People with the gene defect may even be asymptomatic beyond middle age. The similarity of the neuropathology to aggressive multiple sclerosis and the presence of oligoclonal bands in the cerebrospinal fluid has supported the idea that for childhood ALD to occur an autoimmune mechanism is necessary in addition to the genetic defect in VLCFA metabolism. That defect has now been identified as of a specific peroxisomal acyl-CoA synthetase.[17] The site of the gene on Xq28 is adjacent to the genes for red and green colour blindness which may be simultaneously deleted.[18]

Defects of β oxidation. 'pseudo-Zellweger syndrome', 'pseudo-NALD', etc

In normal VLCFA metabolism the acyl-CoA synthesised by the enzyme deficient in ALD is oxidised by three peroxisomal enzymes in sequence: acyl-CoA oxidase ('oxidase'), bifunctional protein, and 3-oxoacyl-CoA thiolase ('thiolase').

The first disorder now known to lack one of these enzymes was originally labelled pseudo-Zellweger syndrome[19]: it was later discovered that the child in question lacked only the protein of the thiolase enzyme.[20] The clinical and pathological features resembled Zellweger syndrome except that dysmorphic features were not so appreciable and there was no calcific stippling. A further family has been described[21] in which although the thiolase protein was present as shown by immunoblot, the duodenal bile acid pattern indicated thiolase deficiency and was identical to that of the infant with pseudo-Zellweger syndrome (PT Clayton, personal communication). Except for the huge fontanelle (in keeping with a severely delayed bone age), dysmorphic signs were slight in this family (figure). In a further child with evidence of thiolase inactivity, calcific stippling of the patellae was present (MD King, personal communication). All of these infants had neonatal onset seizures and profound hypotonia (figure).

Isolated deficiency of the oxidase protein leads to a clinical course like NALD, entitled pseudo-NALD.[22] Pseudo-NALD was also the name given to the condition of a similar patient in whom the pathology also resembled NALD.[23] Later, the oxidase protein was found to be present,[24] but presumably it is present in an inactive form.

The last of the three selective β oxidation disorders, bifunctional protein deficiency, has now been discovered (HW Moser, personal communication) in a patient with 'clinical clues' (see below).

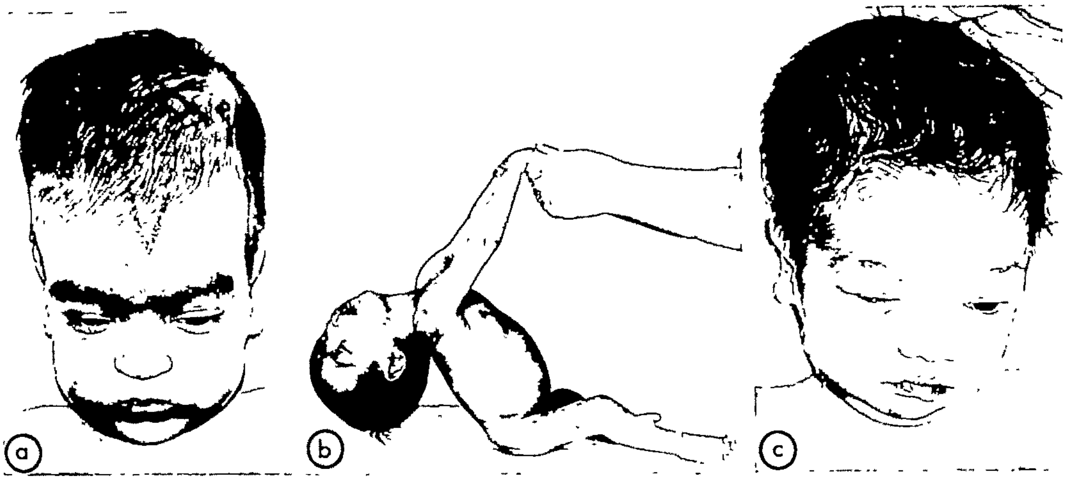

Figure *Siblings with defective thiolase (a) fontanelle and high forehead aged 3 months, (b) extreme neck hypotonia (same day as (a)); and (c) brother aged 1 week, dysmorphism minimal. Note need for hand support in supine position in (a) and (c)*

Refsum disease (group 3B)
The only reasonably established group 3B disorder affecting the nervous system is Refsum disease which with retinitis pigmentosa, neuropathy, and deafness may present in mid childhood. Here the isolated defect is of (presumed) peroxisomal phytanic oxidase.

Clinical clues to a possible peroxisomopathy

Pointers to one or other peroxisomal disorder include: large fontanelle, absent ear lobules, neck hypotonia, early seizures, developmental standstill delay or arrest, pigmentary retinopathy (with a low ERG), sensorineural deafness (with low BAER), hepatomegaly (with or without fibrosis), unexplained hypocholesterolaemia or hypovitaminosis E, and calcific stippling of epiphyses.

Tests in suspect patients

Measurement of the enzyme DHAP-AT in fibroblasts or thrombocytes should detect all the generalised peroxisomal disorders (group 1),[25] and those in group 2. The concentration of VLCFA is raised in plasma and fibroblasts in all the generalised peroxisomopathies (group 1) and in all those in group 3A Abnormal bile acids in urine,[26] plasma,[27] and bile should be detected (at any rate in the young patient) in all of group 1; in those with absent or defective thiolase the pattern is different and may be specific. Bile acids are normal in ALD and in oxidase deficiency; the situation in bifunctional protein deficiency is not yet known. A properly prepared liver biopsy specimen in group 1 will show absent or grossly deficient peroxisomes, whereas in group 3A many of the peroxisomes are large (up to 1 µ)[19 21 22 24] and they may be odd shaped. Phytanic acid is of course raised in the plasma in Refsum disease, but after infancy it will be raised in all the ('mild') group 1 disorders and in RCDP.

Treatment

Specific therapeutic possibilities are at present limited except in Refsum disease where low phytanic acid diet with or without plasmapheresis and low fat diet has proved effective. Low phytanic acid diet has also been used in two children with mild group 1 disorder ('infantile Refsum').[28] The neurological improvement reported, including possible arrest of progressive neuropathy, needs confirmation by further studies. However, as in all chronic disorders affecting the nervous system, non-specific treatment (for example, phenytoin for seizures) may help. More specifically, vitamin E supplementation is reasonable in those older children with a secondary deficiency. Attempts to abort ALD by the rigorous low VLCFA diet, oleate and erucate supplements, and plasmapheresis have not yet shown convincing benefit. When there is an affected family member, prevention is possible in all the group 1, 2, and 3A disorders, in that early prenatal diagnosis can be made by DHAP-AT analysis in groups 1 and 2 and by VLCFA measurements in groups 1 and 3A.

I would like to thank Peter Barth, Guy Besley, Peter Clayton, David Doyle, Brian Harding, Brian Lake, Mary King, Ann Moser,

Hugo Moser, Bwee-Tien Poll-The, Frank Roels, Ruud Schutgens, John Toomie and Ronald Wanders for helpful discussions and insights.

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Clinical significance of IgG subclass deficiency

IgG is quantitively and functionally the major class of immunoglobulin found in serum and all extravascular fluids except mucosal secretions Four structurally and functionally distinct subclasses (IgG 1 to 4) have been described in man.[1] Deficiencies of individual subclasses of IgG were first described almost 20 years ago,[2] but their exact prevalence and significance is not accurately known.[3] They do appear, however, to be relatively common—possibly more common than IgA deficiency which occurs in 1:500 of the healthy population.[4] As with IgA deficiency, asymptomatic individuals are found both in blood donors[5] and among the relatives of patients with a variety of immunodeficiencies, including family members of patients with IgG subclass deficiencies.[6]

The different functions of individual IgG subclasses are partly related to their structure; only IgG 1 and IgG 3 effectively fix complement and similarly there is variability of crystallisable fragment (Fc) receptor binding to different leucocyte populations. Although antigenic stimulation may potentially give rise to antibody of any IgG subclass, usually it is restricted to one or two subclasses depending on the type of antigen.[7] IgG 1 and IgG 3 generally provide the response to protein antigens of bacteria, viruses, vaccines, and foods. IgG 2 antibodies are predominantly to carbohydrate antigens and are important in protection against polysaccharide encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis.*[7] In infants and children of less than two years of age, however, the anticarbohydrate response is predominantly in the IgG 1 subclass which is possibly less protective, accounting for the increased susceptibility to invasive disease by encapsulated organisms. The *H influenzae* polysaccharide vaccine produces little or no protection in these children,[8] but by conjugating the polysaccharide to a protein carrier a protective immune response may be obtained.[9] It is not known whether this is due to a change in the IgG subclass of the antibody response to the vaccine. The role of IgG 4 is controversial. It is produced in response to repeated antigenic stimulation and it has been suggested that it may act as a blocking antibody in parasitic[10] and allergic[7] diseases or paradoxically be responsible for mediation of allergic responses.[11 12]

The mechanisms underlying IgG subclass deficiency are not clear. Deletions of sections of the immunoglobulin gene are extremely rare but have been found in a few healthy individuals with deficiencies of more than one IgG subclass in combination with IgA 1 deficiency.[13] Such deletions, however, have not been shown in symptomatic individuals with IgG subclass deficiency, nor have isolated deletions of single IgG subclass heavy chain regions been found.[14] The defect therefore probably resides at the level of regulation of immunoglobulin gene expression in B-lymphocytes. In some cases this may be due to abnormal T-lymphocyte control of B-lymphocyte function—IgG subclass deficiencies are often found in patients with T-lymphocyte deficiencies including AIDS[15] and after bone marrow transplantation.[16]

Among children with IgG subclass deficiencies there is 3:1 male:female predominance with IgG 2 deficiency being most common. This situation is reversed after puberty, women with IgG 3 deficiency becoming more common.[17] IgG subclass deficiencies may be transient in childhood, as seen with IgA deficiency. There appears to be more variation, however, in the levels of IgG subclass deficiency and more associations with other immunodeficiencies are found.[16] Low concentrations of IgG subclasses should be interpreted with caution before the age of 2 years as 'transient hypogammaglobulinaemia of infancy'[18] is relatively common and because of the late maturation of IgG 2 and IgG 4 immunoglobulin concentrations and antibody responses [7]

IgG 1 to 4 respectively constitute 65%, 25%, 7%, and 3% of total serum IgG. In consequence deficiencies of IgG 2, 3, or 4 may occur in the presence of normal concentrations of total serum IgG. In fact high total concentrations of IgG may be found when as a result of one IgG subclass deficiency persistent stimulation of the other subclasses by repeated or chronic infection or inflammation occurs In this situation even IgG 1 deficiency may occur in the presence of a normal total IgG.

Patients with IgG subclass deficiency are characterised by a vast array of symptoms and disease associations which are listed below.

(I) RESPIRATORY TRACT INFECTIONS

Recurrent or severe upper respiratory tract infections, otitis media, sinusitis, and bronchopulmonary infections are the most common manifestation of IgG subclass deficiency.[6 19] They occur particularly in IgG 2 deficiency, but also in IgG 1 and IgG 3 deficiency. Organ damage resulting in deafness and bronchiectasis may occur, particularly when associated with IgA deficiency.[20] Occasionally organ damage may occur without symptoms of major infection being evident.

(2) GASTROINTESTINAL SYMPTOMS

We have observed a number of patients with diarrhoea, failure to thrive, and a variety of IgG subclass deficiencies, some of whom responded to intravenous immunoglobulin (IVIg) treatment. Similar symptoms were attributed to infection in another group of patients who also responded to IVIg.[21] Gastrointestinal symptoms may however, be related to food intolerance in some cases.[17]

(3) OTHER INFECTIONS

Osteomyelitis, meningitis, urinary tract infection, and septicaemia are all described in patients with IgG subclass deficiencies. They may also have recurrent bacterial and viral (*Herpes simplex*) cutaneous infections.[6]

(4) ATOPY

A high incidence of significant allergic disease among people with IgG subclass deficiency has been noted,[17 22] particularly in IgG 3 deficiency[5 16]; IgG 4 concentrations may be reduced or raised, sometimes to very high levels.

(5) MULTISYSTEM DISEASE AND AUTOIMMUNITY

A number of groups have described associations of IgG subclass deficiencies with vasculitide including Henoch-Schönlein purpura, autoimmune cytopenias, and diabetes mellitus type I.[23 24] As with atopy it is unknown how and if IgG subclass deficiencies predispose to these disorders. The aetiology may be related to either a primary problem of dysregulation of immunity, or one which is secondary to frequent or abnormal handling of infections.

(6) NEUROLOGICAL DISORDERS

Three groups have described a remarkable response of severe anticonvulsant resistant epilepsy to intravenous immunoglobulin treatment.[25–27] About half of these patients had IgG subclass deficiency, and we have observed similar responses in two subclass deficient children with intractable fits.[16] Prospective studies in several centres are in progress to try and elucidate this phenomenon. IgG subclass deficiency is found in association with Freidreich's ataxia and ataxia-telangiectasia.

(7) ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Despite the hypergammaglobulinaemia characteristic of infection with human immunodeficiency virus 1, many patients have significant abnormalities of antibody production, and may be deficient in one or more IgG subclass.[15]

(8) OTHER IMMUNODEFICIENCIES

IgG subclass deficiency is often associated with IgA deficiency[4] and patients with this combination of immunodeficiencies usually have more symptoms and evidence of organ damage than those who have only one deficiency.[20] Patients with severe combined immunodeficiency, chronic granulomatous disease, and deficiency of major histocompatibility antigens (bare lymphocyte syndrome) may have low IgG subclass concentrations.[16 21]

(9) MISCELLANEOUS

Subclass deficiencies have been noted in both the early and late stages of recovery from bone marrow transplantation for immunodeficiency[28]—the immunoglobulin subclass concentrations of the donors are usually normal, giving further evidence for the role of dysregulation in the generation of IgG subclass deficiencies. Certain patients with pyrexia of unknown origin have been found to have IgG subclass deficiency, some of whom were characterised by marked lymphadenopathy and response to immunoglobulin infusions.[16]

The measurement of IgG subclasses and the interpretation of low concentrations may present considerable difficulty. There is a major variation of concentration with age, and establishing normal ranges presents major problems. There may also be inconsistency between and within different assays.[3] Faced with the problem that it may be difficult to interpret the finding of a low or even undetectable IgG subclass concentration in an individual, patients should be treated according to their symptoms and signs along the lines suggested for IgA deficiency.[4] The combination of judicious further investigation, observation, and escalation of preventative treatment (if required) should benefit most patients and allow identification of the minority who would benefit from intravenous immunoglobulin (IVIg) treatment. As IVIg can occasionally cause anaphylaxis[29] and transmit non-A non-B hepatitis,[30] the decision to prescribe it should only be taken after thorough evaluation of both the patient and other therapeutic options.

Finally, it is worth remembering that IgG subclass measurements are not the 'last word' in assessment of humoral immunity. Despite having normal concentrations of all immunoglobulin class and subclasses, patients have been reported who fail to mount a protective antibody response to certain infections[31]—the quality of the immunoglobulin is probably as important as its quantity.

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Rising asthma admissions and self referral

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SUMMARY An eight fold rise in asthma admissions to the Royal Alexandra Hospital for Sick Children, Brighton occurred over the 15 year period 1971–85. The cause was an increase in the number of children seen, rather than increased readmission. The initial rise was associated with the introduction of nebulised salbutamol in 1976. The children concerned were mainly over 5 years old. Three years later came a larger influx of younger children. Circumstances leading to admissions were examined in a prospective study over a one year period. There were 605 admissions, 437 (72%) were self referrals. The commonest reason parents gave for preferring hospital treatment was the availability of nebuliser treatment.

A 167% rise in child asthma admissions in the South West Thames region between 1970 and 1978 was described by Anderson *et al.*[1] He found that there had been a shift in the balance of care towards the hospital largely caused by an increase in self referrals. There was little change in the severity on admission, and an inadequacy of ambulatory care was postulated. Khot *et al* found that admissions for the whole of England and Wales had trebled between 1975 and 1981.[2] The similarity of the monthly profiles, nationally, suggested the operation of 'major trigger factors.' Mitchell reviewed international trends in 1985 and found a striking rise in all countries examined.[3] Although the major change was the increase in the number of individual patients admitted, he concluded that a rise in asthma incidence could only account for part of the increase.

Increased admissions for asthma may result from increased incidence or severity of disease, an increased tendency to seek medical help for conditions previously tolerated, increased hospital referral by general practitioners, increased self referral to casualty departments, or an increased tendency of medical officers to admit.[4] Child asthma admissions in the Brighton area have risen as elsewhere, and have continued to rise. Criteria for admission in Brighton have not changed: children are admitted when symptoms or poor response to bronchodilator treatment indicate that intensive treatment or observation are required. Two surveys were therefore undertaken: a retrospective survey of admission trends and changes in management, and a prospective survey over a one year period to investigate the frequency of self referral and parental expectations of hospital treatment.

Methods

RETROSPECTIVE SURVEY

Details of all asthma admissions to the Royal Alexandra Hospital for Sick Children, Brighton were obtained from Hospital Activity Analysis for the years 1973–85. The data consisted of dates of birth, admission and discharge, sex, and hospital number, permitting identification of individual patients. The data were transferred electronically to a BBC microcomputer for analysis and numbers were checked for accuracy against existing hospital records. Rates per 1000 population allowed for admissions from outside the area. Data for 1971 and 1972 were derived from hospital records. For comparison, data were obtained from hospital records on admissions for bronchiolitis and wheezy bronchitis.

Information on treatment in hospital was known for all patients in 1985; for previous years it was derived from a sample of hospital notes covering 496 admissions. Random selection in each year was attempted but is not guaranteed owing to missing notes. Larger samples were used for years of changing trends: sampling was continued for each year until a set of stable averages was obtained, and accuracy was checked by the jackknife (data splitting) technique. Also obtained was information on casualty attendance (from 1975 onward) and on overall admission rate (from 1973).

The data for admission were sorted by date of admission, and by patient in order of date of birth. Identification of individual children provided, among other things, data on readmissions. The following definition of readmission rate was chosen so that trend could be examined over the longest possible time period: this was the percentage admissions in a calendar year where there had been a previous admission in the past natural year A 60% readmission rate would therefore indicate that 60% had a previous admission within 365 days

Trends for admission rate, age distribution, length of admission, and hospital treatment were calculated and plotted by computer. Significance was determined from the standard error except for admissions where the χ^2 test was used. Temporal associations were explored by multivariate analysis and plotting residuals allowing, for example, change in median length of admission to be examined after accounting for the possible effects of changes in therapeutic practice.

PROSPECTIVE SURVEY

Data were collected prospectively on children with asthma admitted in the one year period March 1985 to March 1986 There were 605 admissions. Parents of 386 of the children who were admitted (64%) were interviewed in person by EB or JS, the use of two interviewers directly concerned in the study was unavoidable The remaining parents were sent a postal questionnaire which 135 returned and 84 did not Data were therefore available on 521 (86%) The questionnaire covered past, current, and family history, medication, contact with general practitioner, and expectations of hospital treatment Parental expectations were determined as far as possible without leading questions.

Results

RETROSPECTIVE STUDY

An eight fold rise in admissions occurred over the entire period 1971–85 (fig 1) The rise occurred in two stages. first a moderate rise in admissions of school age children (fig 2a), and later a massive rise in children of preschool age (fig 2b) The age profile underwent an appreciable change as a result (fig 3). Median age rose from 5·3 to 7·1, then fell to 4·4 years.

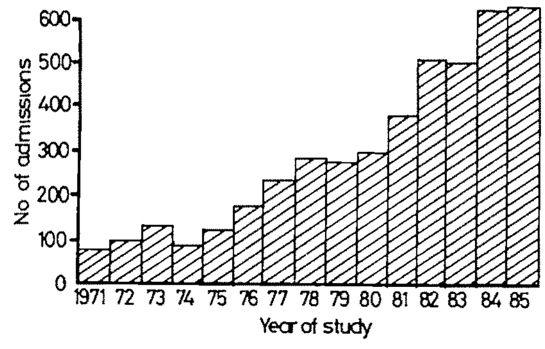

Fig 1 *No of children with asthma admitted to the Royal Alexandra Hospital each year*

The initial rise, which started in 1976, closely followed the introduction of nebulised salbutamol. This advent had a considerable effect on other treatment (fig 4) Oral bronchodilators were rapidly supplanted, and the use of croupettes and medications having a sedative effect (promethazine, trimeprazine, chloral, chlorpromazine, phenobarbitone) declined sharply Corticosteroid use fell from over 50% to 10%, with a gradual recovery to about 30% over several years.

The rise in admissions of younger children followed a similar pattern to that of the older children, but was larger, and occurred more than three years later There was no obvious contemporary precipitating factor. An increasing use of the hospital casualty department for all conditions was evident in attendance rates over the period: 2823 in 1975, 3595

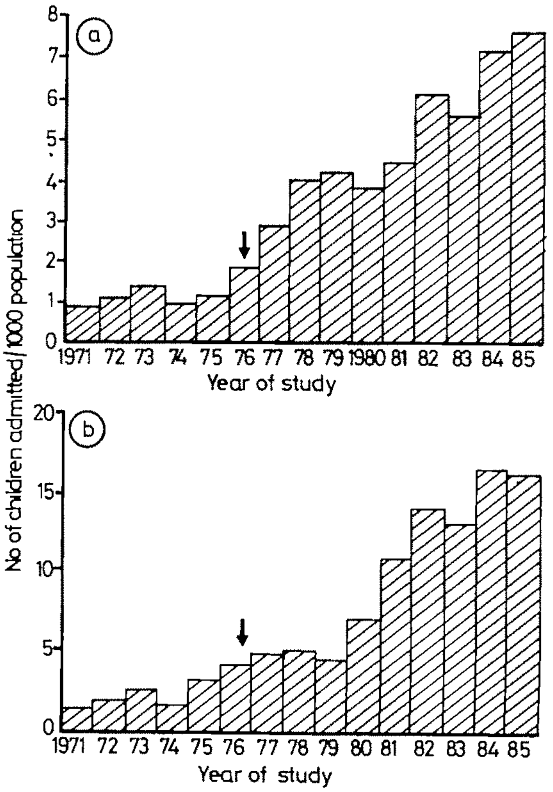

Fig 2 *No of children aged (a) 5–14 years and (b) 0–4 years admitted per 1000 population in the same age range The arrow indicates the 50% point in the introduction of nebulised salbutamol*

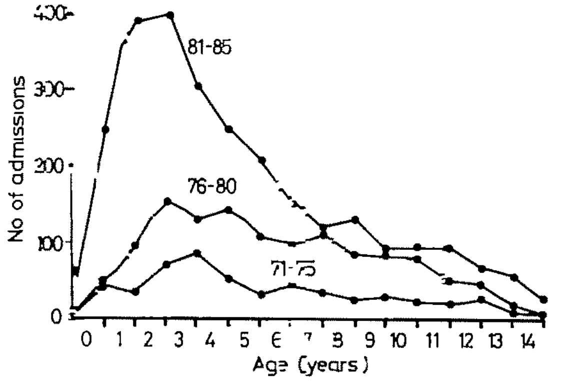

Fig 3 *Changing age distribution for admissions for asthma in three five year periods. 1971–5, 1976–80, 1981–5 Rising admissions are evident, as well as a noticeable increase in the number of younger children admitted in the most recent period*

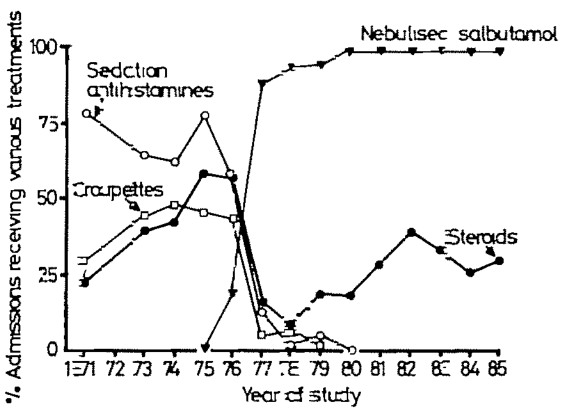

Fig 4 *Percentage of admissions for asthma receiving nebulised salbutamol in each year and associated changes in other treatments. Steroids were either hydrocortisone or prednisolone*

in 1980 and 5166 in 1985 The age distribution of non-asthmatic children, however, did not show any consistent change, the median age remaining constant at 16 months.

The rise in asthma admissions was almost entirely due to an increase in the number of asthmatic children presenting to hospital: there was a similar eightfold rise in the number of first admissions for asthma each year. The readmission rates for children over and under 5 years were about 15% and 58% (the difference reflects the greater frequency of wheezing attacks in younger children), and there was no overall rising trend Readmissions, however, did account for some of the initial rise after the introduction of nebulised salbutamol. The rate in children over 5 rose from 43% in 1976 to about 60% in the next three years and then fell There was a lesser but similar initial trend in the later influx of younger children, mainly affecting those aged 3 or 4 when they first received nebuliser treatment.

There was no artefact due to diagnostic transfer: admissions for wheezy bronchitis remained at a relatively constant and low level, with an increasing tendency over the years for the seasonal pattern to mirror that of bronchiolitis. There was no increase in the proportion of asthmatic children admitted from casualty; it was not, however, possible to determine whether children with milder symptoms were being admitted, as it was not known whether children were presenting with a similar or milder range of disease than previously. The median duration of stay for asthma admissions fell over the period from 4·3 to 2·2 days but the trend was evident before any rise in admissions, and varied with steroid and nebuliser use. Admissions were not drawn from a wider area or from an altered geographic distribution.

PROSPECTIVE STUDY

There were 605 admissions (407 boys, 198 girls) over the one year period; a further 39 children were sent home from casualty Out of a total of 455 children, 369 (61%) admissions were of children admitted only once during the study period; 47 children (10%) were admitted twice, and 39 (9%) three or more times. The median (1st and 3rd quartile) age was 4·2 (2·4–6·9) years. Children stayed in hospital for a median three (two to three) days, and received nebulised bronchodilator on a median eight (five to 12) occasions. Additional treatment with steroids was given to 185 out of 605 (31%).

Self referrals accounted for 437 out of 605 (72%) admissions, or 351 out of the 521 (67%) answering the questionnaire Parents of 284 (55%) of these children had not consulted their general practitioner at any time during the current illness, and of these, 218 (77%) quoted knowledge of an open access policy for asthmatics as their reason for bringing the child to hospital Most of the remaining consultations were accounted for either by the severity of the child's condition (5%), or a reported telephone instruction from the general practitioner to take the child to hospital (9%).

Altogether 136 admissions were first admissions for asthma. Of these, 116 (85%) had seen their general practitioner earlier in the illness and of these 92 (79%) were referred. Where there had been a previous admission the proportions were 121 out of 385 (31%) and 78 out of 121 (64%). Of the 237 out of 521 (45%) who saw their general practitioner, 197 (83%) saw their own practitioner rather than a

Table *Treatment received from general practitioner*

	*No (%) of children treated** *(n=160)*
Nebuliser (general practitioner)	45 (28)
Nebuliser (home)	16 (10)
Inhaler	15 (9)
Injection	7 (4)
Bronchodilator syrup	35 (22)
Antibiotics	35 (22)
Cough syrup	4 (3)
Other	3 (2)

Where more than one treatment was given, only one was recorded the order of preference was the same as used in the table
*Of the 237 children who saw their general practitioner 77 received no treatment

partner or deputy. Only 152 (64%) of the parents remembered being told their child had asthma. Where treatment was given (table) this was thought to be effective in only 51 out of 160 (32%). Nebulised bronchodilator treatment, however, was thought effective in 37 out of the 51 (73%) in contrast with other treatment, which was thought effective in only 14 out of 99 (14%). When the child had not been referred directly to hospital by the general practitioner, the median (1st and 3rd quartile) time interval between general practitioner and hospital consultations was eight (three to 24) hours. Dissatisfaction with treatment and symptomatic deterioration were the main reasons given for not returning.

In seeking medical treatment 253 out of 424 (60%) of those without home nebulisers were primarily trying to gain access to nebuliser treatment. This applied to 13 of the 133 (10%) children on their first admission and to 240 out of 291 (82%) of those with previous admissions.

Discussion

RISING INCIDENCE

The incidence of asthma has been variously reported as between 0·1% and 19%.[5] Rates vary with the time of survey and population described, but in particular with definition and method adopted. Rates approach 25% as the definition is expanded to include children with as few as one or two wheezing episodes. This incidence has shown little change over almost 30 years.[6-9]

The possibility of a rising incidence of asthma in children of school age was considered as long ago as 1954.[10] A rise was confirmed by serial studies in Birmingham: 1·76% in 1956–7, 5·4% in 1968–9, and 6·34% in 1974–5.[11] The incidence is now thought to be as high as 11%.[8 12] Further evidence comes from rising admissions,[1-3] general practice consultations,[13] and deaths.[14 15] It may, however, be the severity rather than the incidence which is rising. A number of environmental changes and their effects may indirectly account for this warmth and humidity on house mite populations, travel on viral spread, farming practices on pollen and fungal spore release, and motor vehicles and power stations on air pollution, etc. As potential factors are so numerous and may show similar trends, proof may be difficult to obtain, particularly retrospectively.

This study documents an appreciable rise in asthma admissions, a phenomenon that may result from increased incidence, diagnosis, or severity of asthma, but which may also reflect altered referral patterns or expectations of care.

DEFINITION OF ASTHMA

The high incidence of episodic wheezing in early life, and the tendency for this apparent reaction to viral upper respiratory tract infection to disappear by the age of 5 years, led to a past recommendation not to regard such children as asthmatic.[16] The problem of definition, however, remains as there is no clear dividing line between asthmatic and non-asthmatic wheezing.[12] The likelihood is that early wheezing is part of the already wide range of disease known as asthma.[17] Children are prone to viral infections, in asthmatic children these provoke episodic wheezing, and much confusion has resulted. The quest for a formula indicating which children will grow out of their asthma may likewise prove a false goal,[9 18] as it is now known that many of these children have persistent abnormalities of lung function and risk developing chronic obstructive lung disease in later life.[19 20]

Definitions of asthma hinge on the concept of reversibility,[21 22] and in children the impact of the nebuliser, and other effective bronchodilator delivery systems, may have been considerable. The practical diagnosis of asthma has been immensely simplified: if wheezing responds then it is asthma. Theoretical difficulties remain as bronchodilators treat only one component of airway narrowing,[23] and are known to be less effective in young children.[24]

Conceptual changes such as these may have broadened the definition of asthma. There is no evidence from this or previous studies, however, that diagnostic transfer has caused an apparent rise in asthma admissions. The numbers of children admitted with a diagnosis of bronchitis have always been too small and constant for this to have occurred. The same may not be true, however, for children who wheeze in the community. Many studies have publicised the underdiagnosis and undertreatment of asthma[25 26] and the disservice provided to parents by not telling them the diagnosis.[25] The availability of effective treatment may also have resulted in an increased willingness to diagnose asthma

THE EFFECTS OF NEW MEDICATIONS

The nebuliser caused a revolution in the inpatient treatment of asthma. After its introduction the use of ineffectual treatment rapidly died out. Steroid use also fell, but inappropriately. It is interesting to speculate that a similar temporary fall in steroid use may have contributed to the rise in asthma deaths which followed the introduction of bronchodilator inhalers in the 1960s.[27]

The yearly change in asthma admission rate was strongly associated with the introduction of nebulised bronchodilator treatment. Because this was an abrupt change, unrelated to environmental and social factors, the chance of a spurious association is reduced. Initially there were increased readmissions, probably as a reaction to the availability of more effective treatment. The increase in readmissions was a temporary phenomenon, and may have been reversed by improvements in outpatient treatment. The possibility of a reduced threshold for admission cannot be excluded, but an explanation is required for the vast increase in numbers of patients presenting to casualty with asthma.

The later part of the rise was characterised by an appreciable rise in the number of preschool children. When viewed separately this rise does not show the same relation with the introduction of hospital nebulisers. Preschool children have the most to gain from nebuliser treatment as few will be able to use inhalers. Their increased admissions may reflect the more gradual acquisition of nebulisers by general practitioners, who still provide the usual route by which children are introduced to hospital.

Nebulised bronchodilator treatment provides rapid symptomatic relief. This may have had the effect of attracting children to hospital; they often tell their parents to bring them when they are wheezy. Because of the likelihood that wheezing will return within a few hours children are usually admitted. Children given a nebulisation by their general practitioner are often subsequently referred to hospital for the same reason. Many have by now learned, however, to bypass their general practitioner and come direct to hospital. This may have been a major cause of the rise in number of asthmatic children seen.

It is clear that parents of asthmatic children are dissatisfied with the treatment they receive from their general practitioners and in consequence they seek hospital treatment. Once parents and children have experienced treatment in hospital they tend to return. Hospital treatment is seen as superior primarily in respect of providing regular nebulised bronchodilator treatment. Many general practitioners do not possess nebulisers. Only 22% of children were given nebuliser treatment by their general practitioner; one quarter used the child's own home nebuliser.

Strong preference for nebuliser treatment may also explain the willingness of parents of asthmatic children to travel greater distances to hospital. Although the median (1st and 3rd quartile) distances travelled by self referring parents of asthmatic (3·7; 1·8–11·4 km) and other children (3·0; 1·5–4·5 km) were similar, the upper quartile for the asthmatic children was very much larger and the two distributions differed very significantly ($p<<0 \cdot 0001$ Wilcoxon rank sum test).

AGE DISTRIBUTION

The initial rise in admissions consisted predominantly of school age children, followed later by a greater rise in preschool children. It is unlikely that this represents a change in the pattern of wheezing in the community. Past studies have shown that there are more younger than older children who wheeze, and they do so more often.[28] If the proportion of wheezing episodes resulting in admission has risen, then the age distribution of admissions may increasingly have come to mirror that of wheezing in the community.[13] The increased presentation of children with a short history of wheezing may have resulted from increased diagnosis or increased public awareness of asthma. Alternatively, improvements in prophylactic treatment and drug delivery systems may have prevented a greater rise in admissions of older children, whereas similar treatment may be impractical or ineffective in preschool children.[24]

REVERSING THE TREND

Admission for asthma is rarely desirable, although there may be indirect benefits such as peace of mind for all concerned and an opportunity for patient education. Admission is often highly disruptive to family life, and places a strain on hospital resources. It transpires, however, that most patients are self referrals, and many expect admission.

As the major reason for self referral appears to be access to nebuliser treatment, greater provision of nebulisers at home may help reduce admissions. Home nebuliser treatment, however, may not be without risk.[29] It is highly desirable that more general practitioners should own nebulisers. As few attacks of asthma will remit after a single treatment, nebulisers need to be made available for short term loan. Potential problems are unfamiliarity with the machine, and inability of parents of newly diagnosed children to judge deterioration or inadequate response to treatment.

Improved outpatient management may help to reduce admissions, but this is probably already occurring. The main problem is the large number of first admissions, and the large proportion of very young children with asthma in whom administration of treatment may be difficult, and response less satisfactory. Wheezing in children tends to be episodic, and the early use of oral steroids, in conjunction with other treatment, has been shown to be highly effective.[30] There seems to be a great reticence in general practice to use short oral steroid courses and it seems likely that if this attitude could be altered together with acceptance of sensible controlled nebulised bronchodilator treatment in the home many hospital admissions could be avoided.

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Simplified oral pancreatic function test

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SUMMARY The standard Bentiromide test and a new modified test using p-aminosalicylic acid (PAS) as a pharmacokinetic marker for p-aminobenzoic acid (PABA) have been evaluated in the detection of pancreatic exocrine insufficiency in children. The conventional two day test using a colorimetric assay for urinary PABA discriminated poorly between five children with pancreatic insufficiency and 13 others with normal pancreatic function. Two further groups of patients, comprising 28 with pancreatic exocrine insufficiency and 20 with normal pancreatic function underwent the modified test, and urine samples were analysed by high performance liquid chromatography. The results showed a complete separation between groups. The use of PAS eliminates a number of sources of error inherent in a two day Bentiromide test and provides a simplified and accurate diagnostic test for pancreatic insufficiency. The PABA-PAS modified test enables collection of the urine to be done during a single six hour period.

Exocrine pancreatic insufficiency is often considered in the differential diagnosis of failure to thrive, protracted diarrhoea, or steatorrhoea. Though it is most commonly seen in patients with cystic fibrosis, it may occur in a number of other disorders.[1] Duodenal intubation followed by hormonal stimulation of the pancreas with intravenous pancreozymin and secretin is still considered the most reliable test for the diagnosis of pancreatic exocrine insufficiency. This test is, however, unpleasant for the patient subsequent laboratory analysis is both time consuming and complex, and reliable supplies of secretin are difficult to obtain

Simple screening tests for pancreatic insufficiency have therefore been developed and evaluated largely in adult patients as alternatives to duodenal intubation.[2] The Bentiromide test has been most widely evaluated and relies on hydrolysis of an orally administered synthetic compound N-benzoyl-l-tyrosyl p-aminobenzoic acid (Bentiromide) within the small bowel. This compound is cleaved selectively by pancreatic chymotrypsin to release p-aminobenzoic acid (PABA). PABA is absorbed in the small intestine, conjugated in the liver, and excreted in the urine. The amount recovered from a timed urine collection expressed as a proportion of the PABA given in the dose of Bentiromide gives an indication of duodenal chymotrypsin activity and hence of exocrine pancreatic function. False postive results may occur, however in patients with disordered gut motility or an enteropathy (which result in low PABA absorption) or in those with hepatic or renal dysfunction, when either conjugation or urinary excretion of PABA may be reduced.[3] In addition, drugs such as paracetamol and sulphonamides, or certain foods, may interfere with the urinary assay of PABA.

An attempt to correct for these variables has been reported whereby a dose of free PABA alone is given the day after the Bentiromide test A PABA excretion index is then derived by dividing the amount of PABA recovered on day 1 by the amount recovered on day 2. This makes the test more cumbersome but can improve specificity[4] by reducing the number of false positives. Subsequent refinements have included administration of PABA labelled with ^{14}C at the same time as the Bentiromide,[5] which avoids the need to repeat the test on a second day. Though it is undesirable to give the β emitter ^{14}C to children in a diagnostic test, the single day test with ^{14}C PABA has gained acceptance as a screening test for pancreatic disease in adults.[6]

As an alternative to ^{14}C PABA we have evaluated the use of a structural analogue of PABA, p-aminosalicylic acid (PAS), and compared the initial PABA excretion index obtained with ^{14}C PABA with that using PAS. The advantage of using PAS is that it is structurally and pharmacokinetically related to PABA and is safe. Furthermore, after low doses, its concentration in urine can be measured simultaneously with PABA by high performance liquid chromatography. The comparison of PABA excretion index obtained using ^{14}C PABA and then PAS in a group of adult patients with a wide range of pancreatic exocrine function showed a high correlation (r=0·96) confirming the pharmacokinetic similarities of PABA and PAS.[7]

We have therefore assessed the ability of the test incorporating PAS to discriminate between normal and abnormal pancreatic function in children, and have compared our experience with the conventional two stage Bentiromide and free PABA test

Subjects and methods

UNMODIFIED TWO STAGE TEST

Five children with clinically apparent pancreatic insufficiency were investigated. Two had greatly decreased duodenal pancreatic enzyme secretion in response to pancreozymin and secretin stimulation (one had inflammatory bowel disease and one had cystic fibrosis), and two had undergone pancreatectomy and had almost undetectable faecal chymotrypsin. The remaining child had cystic fibrosis and low faecal chymotrypsin concentrations, and was about to start pancreatic enzyme supplementation for poor weight gain. Their median (range) age was 2½ years (6 weeks–5 years) and weight 13·2 kg (4·8–17·4). Pancreatic enzyme supplements were discontinued 48 hours before the test.

Thirteen other subjects had normal pancreatic function. Nine had duodenal enzyme secretion within the reference range after stimulation by intravenous pancreozymin and secretin carried out during investigation of gastrointestinal symptoms. Four others with symptoms of chronic chest disease were under investigation for suspected cystic fibrosis, but subsequently shown to have normal sweat tests and faecal chymotrypsin concentrations. The median (range) age of the control subjects was 2 years (3 weeks to 13 years) and weight 9 kg (2·9–45·2).

After an overnight fast a urine specimen was taken before the test to determine the presence of interfering substances. Bentiromide 15 mg/kg body weight was then given, together with a standard breakfast of unmodified cows' milk and cornflakes. Babies not yet taking solids were given their usual milk feed. Urine was then collected for the next six hours. Adhesive collecting bags were used for children not old enough to cooperate with voiding. Older children were encouraged to drink fluids of their choice during the six hour collecting period and were allowed to eat lunch. The second phase of the test using free PABA alone (4·5 mg/kg) was performed 48 hours later according to an identical protocol

Urine volumes for the six hours were measured and aliquots of 20 ml frozen at −20 C until analysis. Urinary PABA was assayed by the Bratton and Marshall method for sulphanilamide as modified by Smith *et al.*[8]

MODIFIED ONE STAGE TEST, INCLUDING PAS

Twenty eight children with known pancreatic insufficiency were studied; 25 had cystic fibrosis proved by sweat testing, and had clinical steatorrhoea that had improved when enzyme supplements were given. The remaining three subjects, two with Shwachman's syndrome, and one who had had a pancreatectomy, had abnormally low pancreatic enzyme secretion in response to stimulation with pancreozymin and secretin. The median (range) age was 10 years (1 year 5 months–16 years) and weight 23 kg (8·2–54). Pancreatic enzyme replacements were stopped 48 hours before testing.

Twenty other subjects had normal pancreatic function. Fourteen had been investigated for diarrhoea with or without associated failure to thrive (five had enteropathies on histological examination of jejunal biopsy specimens) and had normal pancreozymin and secretin tests. There were two normal children, and four others who had normal stools but who failed to thrive from a variety of causes Each of these had a negative sweat test that excluded cystic fibrosis, and their faecal chymotrypsin concentrations were within the normal range. Their median (range) age was 2½ years (4 months–11 years) and weight 8·5 kg (3–25).

The test protocol for the second group was similar to that for the first group except that 4·5 mg/kg PAS was given simultaneously with 15 mg/kg Bentiromide and a second day test was not performed. A 20 ml aliquot from the six hour urine collection was stored at −20°C until analysis.

After the alkaline hydrolysis of PABA and PAS conjugates, urine samples were assayed by high performance liquid chromatography as previously described[9]; the technique was modified to measure PABA and PAS simultaneously.[7] In a few patients already receiving antibiotics, problems of interference with the measurement of PABA and PAS were overcome by using a 30×0·3 cm μ-Bondapak column (Millipore Ltd, Harrow, Middlesex) in place of the 15×0·5 cm polymer column previously described.[9]

Results from patients with pancreatic insufficiency were compared with those from subjects with pancreatic sufficiency by the Mann-Whitney U test. Because results for the control group in the six hour test were non-parametrically distributed, logarithmic transformation of the data permitted calculation of the mean and two standard deviations as a reference range.

Approval for the study was obtained from the research ethical committee of the Central Birmingham Health Authority. Informed parental consent was obtained before the tests.

Results

The results of the two stage unmodified Bentiromide test are shown in fig 1. The median PABA excretion index for patients with exocrine pancreatic insufficiency was 29 (range 2–65) and for subjects with normal pancreatic function 60 (range 30–118, $p<0·05$) showing considerable overlap between the groups.

The results of the six hour PABA/PAS test are shown in fig 2. The PABA excretion index is derived from the ratio of concentrations of PABA and PAS derivatives in the urine.[7] The median PABA excretion index for patients with pancreatic insufficiency was 19 (range 4–60) and for patients with pancreatic sufficiency 79 (range 66–140, $p<0·0001$) and there was complete separation between the two groups.

The PABA excretion index of the two patients with Shwachman's syndrome were 58 and 60, PABA recovery being 47% and 50%, respectively.

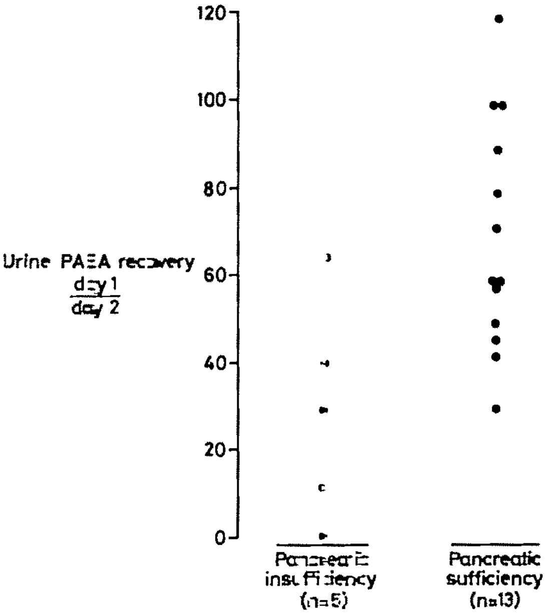

Fig 1 *PABA excretion index results after unmodified two stage Bentiromide test of exocrine pancreatic function.*

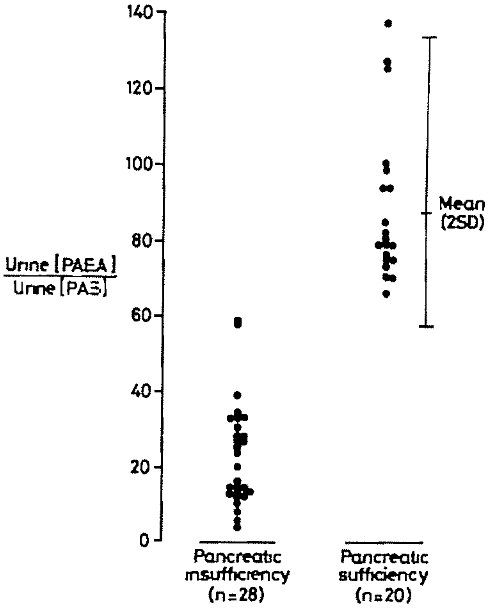

Fig 2 *PABA excretion index results after modified one-stage Bentiromide test of exocrine pancreatic function, incorporating p-aminosalicylic acid.*

Discussion

Results with the unmodified two day test (fig 1) show a wide spread of PABA excretion index in subjects with and without pancreatic insufficiency, with considerable overlap of the two groups. Though the number of patients studied with this test was small, the practical difficulties of a two day procedure and the wide spread of results suggest that it has little clinical application. In contrast, we have found the modified oral pancreatic function test using PAS as a pharmacokinetic marker for PABA a simple and accurate diagnostic test resulting in complete separation between patients with and without pancreatic exocrine insufficiency (fig 2). All patients with pancreatic sufficiency were correctly identified including those children with diarrhoea and failure to thrive secondary to an enteropathy. This makes the test particularly useful for rapid exclusion of pancreatic disease as a cause for altered bowel habit with or without failure of growth. The test also identified 93% of those subjects with pancreatic disease (the patients with Shwachman's syndrome being the two exceptions). Results with the modified test are therefore superior to recently reported findings using fluorescein dilaurate which, when given as an alternative to the

Bentiromide test, produced a false positive result in 20% of control subjects[10]

Patients with the rare condition of isolated lipase deficiency cannot be identified by the Bentiromide test because of its chymotrypsin specificity, nor would an early indication of pancreatic exocrine failure such as decreased bicarbonate secretion be detected. In addition, the test cannot supplant conventional analysis of enzymes in aspirated duodenal juice for studying the ontogeny of pancreatic exocrine function, because it is likely that each pancreatic enzyme has a unique maturational pattern.[11]

The two patients with Shwachman's syndrome, despite almost undetectable duodenal chymotrypsin secretion following pancreozymin and secretin stimulation, were still able to hydrolyse Bentiromide. Anomalous Bentiromide test results in patients with Shwachman's syndrome have been reported before,[12 13] indicating that Bentiromide hydrolysis may not be entirely due to pancreatic chymotrypsin. Sterchi *et al* have characterised a small intestinal brush border enzyme capable of cleaving Bentiromide, and have named it PABA peptide hydrolase.[14] There is a proximal to distal gradient in the activity of this enzyme with the lowest activity in the proximal small bowel. The activity of PABA peptide hydrolase was measured in jejunal biopsy specimens from both the children with Shwachman's syndrome. Interestingly, the child with negligible exocrine function showed the highest PABA peptide hydrolase activity (105·19 μmol/hour/gram of protein; normal control mean (SD): 46·39 (6·97) μmol/hour/gram of protein) whereas the second patient, who had some residual pancreatic function, had lower PABA peptide hydrolase activity (40·79 μmol/hour/gram of protein), within the control range (M Lentze, personal communication). The importance of this finding remains uncertain. Shwachman's syndrome is a rare condition with a number of associated features,[15] making it unlikely that a normal result from a Bentiromide test could in itself lead to misdiagnosis.

Despite these shortcomings the test has a number of clinical applications. It will readily exclude pancreatic exocrine insufficiency in most children being investigated for altered bowel habit, and would immediately call into question the diagnosis of cystic fibrosis if used in patients with a false positive sweat test.[16] In addition, Bentiromide is useful in assessing the effectiveness of exogenous pancreatic enzyme replacement treatment in patients with proved pancreatic insufficiency.[17]

The PABA/PAS modification of the Bentiromide test overcomes a number of problems A single collection of urine over six hours removes differences in completeness of urine collections in the two day test protocol that can be an important source of error. A quick and simple test is particularly useful in children who are not old enough to be able to void urine on demand. The test procedure itself proved acceptable to patients and no adverse reactions were associated with the administration of Bentiromide and PAS.

Using a colorimetric assay, up to 13% of tests fail because of interference from drugs and foodstuffs.[18] Analysis by high performance liquid chromatography reduces this problem, though if patients are receiving antibiotics care must be taken to ensure that this does not interfere with analysis. Apparatus for high performance liquid chromatography is becoming standard in clinical chemistry laboratories, so that this test may be carried out in most district general hospitals. Alternatively, PABA and PAS conjugates remain stable in urine samples at ambient temperature for several days, and could be sent by post to a reference centre.

We recommend that when clinical features suggest pancreatic exocrine insufficiency, consideration should be given to using the modified PABA/PAS test before resorting to more invasive forms of investigation.

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Faecal chymotrypsin: a reliable index of exocrine pancreatic function

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SUMMARY Simultaneous measurements of duodenal and faecal chymotrypsin were made in 30 children aged 3 weeks to 14 years. Apparent chymotrypsin secretion rates measured after stimulation with pancreozymin were compared with the mean faecal chymotrypsin concentration derived from three stool specimens collected at random within 72 hours of the intraduodenal test. In the 25 children who responded to pancreozymin stimulation the mean faecal chymotrypsin concentration was significantly positively correlated with the apparent chymotrypsin secretion rate. Correlation using single specimen stools collected at random was appreciably poorer. In the five children with undetectable or only traces of chymotrypsin in the duodenum after stimulation, the mean faecal chymotrypsin concentrations were only 3–10% of the lower limit of the reference interval. In a second group of 46 children with cystic fibrosis proved by sweat tests and clinical evidence of malabsorption, the chymotrypsin concentration measured in a single stool specimen collected at random was unequivocally subnormal in each case.

Faecal chymotrypsin measurement is a rapid, simple, cheap, readily repeated, non-invasive test of high specificity and sensitivity. Faecal chymotrypsin should be measured before contemplating intraduodenal tests of pancreatic function.

In routine clinical practice pancreatic exocrine function is most accurately assessed by measuring the products of pancreatic secretion in fluid from the upper small intestine.[1] Tests requiring intubation of the intestine are, however, technically difficult, expensive, and invasive and there have been many attempts to find an alternative, particularly for the investigation of children. One approach—the measurement of pancreatic proteolytic enzymes in faeces using pancreatic enzyme specific substrates—has been available for many years[2] but there is still a lack of concensus about its value. Measurement of faecal chymotrypsin has been recommended by some workers[3 4] but other paediatric gastroenterologists discourage it,[5 6] and a firm theoretical basis is required to justify further use of the test. We have therefore sought to validate measurement of faecal chymotrypsin by investigating its performance in two ways firstly by correlating the results with the activities of chymotrypsin and trypsin in the duodenum after stimulation with pancreozymin and secretin, and secondly by measuring its ability to identify the defect in known cases of pancreatic exocrine insufficiency

Subjects and methods

To investigate the correlation between enzyme activities in faeces and duodenal fluid we studied 30 children who were having intraduodenal pancreatic function tests for investigation of gastrointestinal symptoms. Their ages ranged from 3 weeks to 14 years (median 21 months) and weights ranged from 1·8 to 35 kg (median 8·6). Of five children who failed to secrete enzyme after stimulation with pancreozymin and secretin two had Shwachman-Diamond syndrome, one had had a resection of pancreas for nesidioblastosis, one had a pancreatic pseudocyst, and in one the aetiology was unknown. One child with partial insufficiency had inflammatory bowel disease with malnutrition The remaining 24 children were considered to have normal pancreatic function after investigation.

To investigate the ability of the test in patients known to have pancreatic exocrine insufficiency we studied 46 children with cystic fibrosis proved by raised concentrations of electrolytes in the sweat, and clinical evidence of malabsorption

INTRADUODENAL PANCREATIC FUNCTION TESTS

After fasting and sedation with chlorpromazine the children were intubated with a 12 FG nasoduodenal tube that had been modified by removing the end and adding side holes. The tip of the tube was placed at the duodenojejunal flexure under radiographic control. Contamination of duodenal fluid with gastric fluid was prevented by frequently aspirating the stomach through a nasogastric tube. Full details of the technique are given by Tripp *et al.*[7]

The pancreatic function tests were done by a technique similar to that of Hadorn.[8] Fluid was collected by suction over two 10 minute basal secretion periods. Pancreozymin was given intravenously (2 U/kg body weight) and a further two 10 minute fluid collections were then made. This was followed immediately by an intravenous injection of secretin (2 U/kg body weight), and fluid collection was continued for a further three 10 minute periods. Each fluid specimen was placed in a vacuum flask with solid carbon dioxide immediately after collection.

In the laboratory, fluids were kept at −20°C. Chymotrypsin and trypsin were measured within 24 hours of the completion of the test. The duodenal fluid was analysed without any preparation except centrifugation at 3000 *g* for 10 minutes at 4°C to remove insoluble material. Enzyme activities were measured in each 10 minute fluid specimen. Mean concentrations were calculated for the five specimens collected after stimulation with pancreozymin. Secretion rates were calculated by adding the content of the same five specimens and expressing the result as a proportion of body weight. The sampling procedure may have resulted in the loss of some part of the enzyme secreted, so secretion rates were designated 'apparent secretion rate'

STOOL COLLECTION AND PREPARATION

For the 30 children in the first part of the study, three specimens of stool weighing 1–2 g were collected at random on three separate days within 72 hours of the intraduodenal pancreatic function test. Stool analyses were done on samples diluted 1/7 w/w. About 0·5 g stool was first homogenised 1/3 w/w with water using a Potter-Elvehjem pattern glass and Teflon homogeniser with 0·1 mm clearance for maximum dispersion of stool solids. This homogenate was diluted with an equal volume of 0·01 M TRIS buffer, pH 7·8 to produce a final stool dilution of 1/7 w/w. Chymotrypsin activity is adsorbed to the solid phase of faecal homogenates, so care was taken to prepare extremely fine homogenates and to mix them thoroughly before sampling for analysis.

For the 46 children with cystic fibrosis and clinical malabsorption a single stool specimen was collected at random before starting replacement of pancreatic enzymes, or after withdrawal of enzymes replacement for a minimum of 72 hours before stool collection.

ENZYME MEASUREMENTS

Chymotrypsin (EC 3 4.21.1) and trypsin (EC 3.4.21.4) were measured by kinetic, potentiometric methods,[2] in which the rate of hydrolysis of enzyme specific, synthetic substrates (acetyl tyrosine ethyl ester and benzoyl arginine ethyl ester for chymotrypsin and trypsin, respectively) was recorded with an automatic titrator and recorder (Radiometer, Copenhagen). The chymotrypsin and trypsin concentrations were determined using bovine α chymotrypsin (Sigma C4129) and trypsin (Sigma T8642) for the reference standards. The precision of the faecal chymotrypsin analysis was determined by duplicate analysis of 30 faecal samples covering the range 120–1400 μg/g stool. The coefficient of variation was 5·8% The recovery of 25 μg bovine chymotrypsin added to 14 separate faecal homogenates ranged from 90·6–107·8% with a mean recovery of 99·2%.

The bovine α chymotrypsin reference standard had an activity of 0·17 U/μg, the unit being the activity that hydrolysed 1 μmol of acetyl tyrosine ethyl ester in one minute under the conditions described for the method.

Results

DUODENAL FLUID ENZYMES

Of the 30 children studied, 25 responded to the pancreozymin stimulation. Twenty four had apparent trypsin secretion rates above the lower limit of the control range that was defined by Hadorn[8] and confirmed in this department (fig 1), and one was below. In the remaining five tests, the apparent trypsin secretion rates were grossly subnormal with no enzyme activity detectable in three and traces only in two

The apparent chymotrypsin secretion rates were segregated in the same way. The five children who failed to produce a trypsin response after stimulation with pancreozymin also failed to produce a chymotrypsin response. The child that produced a measurable but subnormal apparent trypsin secretion rate also had a subnormal apparent secretion rate of chymotrypsin of only 30% of the lower limit (mean minus 2 SD) of the 24 normal responders. The results of analysis of duodenal fluid therefore ranged from grossly subnormal through partial insufficiency to the physiological range, thereby providing a wide

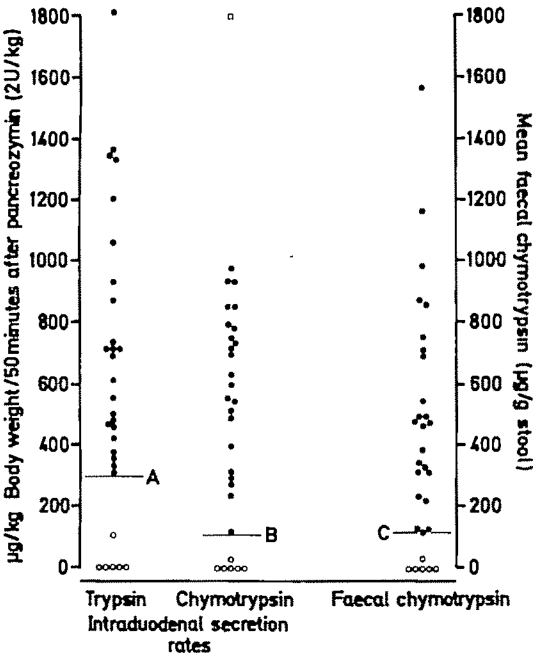

Fig 1 *Apparent rates of secretion for trypsin and chymotrypsin in 30 intraduodenal tests compared with mean faecal chymotrypsin concentrations. Segregation was identical by all three measurements. A=mean minus 2 SD for control subjects*[8]*, B=mean minus 2 SD of data presented but omitting the highest value that was more than 3 SD above the mean, mean (indicated by an open square); C=lower limit of observed range from 150 stool specimens collected at random from 25 healthy infants* ●*=patients with normal response to pancreozymin stimulation, and* ○*=patients with pancreatic insufficiency*

range for identification of a correlation between enzyme activities in duodenal juice and faeces.

FAECAL CHYMOTRYPSIN CONCENTRATIONS

The mean faecal chymotrypsin concentrations were segregated in the same way as the activities in duodenal juice (fig 1) In the five patients with absent or only a trace of duodenal chymotrypsin and trypsin after stimulation, faecal chymotrypsin was also extremely low or absent. The highest mean chymotrypsin in this group was 12 μg/g stool, which was only 10% of the lower limit of our reference range (120 μg/g stool). Of the 25 children with measurable duodenal enzyme activities, 24 had mean faecal chymotrypsin concentrations of 120 μg/g stool or greater. The one child in this group whose results were low (40 μg/g stool, 33% of the lower limit of our reference range) had the subnormal but measurable apparent secretion rates of trypsin and chymotrypsin already mentioned

CORRELATION BETWEEN DUODENAL ENZYME ACTIVITIES AND FAECAL CONCENTRATIONS

In the 25 children who produced measurable enzyme activities in the duodenum after stimulation, mean faecal chymotrypsin concentration showed a highly significant positive correlation with apparent secretion rates of chymotrypsin (fig 2). The Spearman rank correlation coefficient was 0·63 ($p<0·001$). When the apparent secretion rates of chymotrypsin were correlated with chymotrypsin concentrations from single stool specimens collected at random (the initial stool from each triplicate), the correlation only just reached significance ($r=0·43$, $p<0·05$, $>0·025$). Significant positive correlations were also shown between mean faecal chymotrypsin concentration and mean duodenal chymotrypsin concentration, and also between mean faecal chymotrypsin concentration and the apparent secretion rates of trypsin, but the degree of association measured by the Spearman rank correlation coefficient values was less for both correlations (correlation coefficients 0·45 and 0·48 respectively, $p<0·01$).

Using the lower limit of the range of control apparent secretion rates for trypsin or chymotrypsin and the lower limit of the faecal chymotrypsin reference range to define the boundary between normal and abnormal pancreatic function, none of

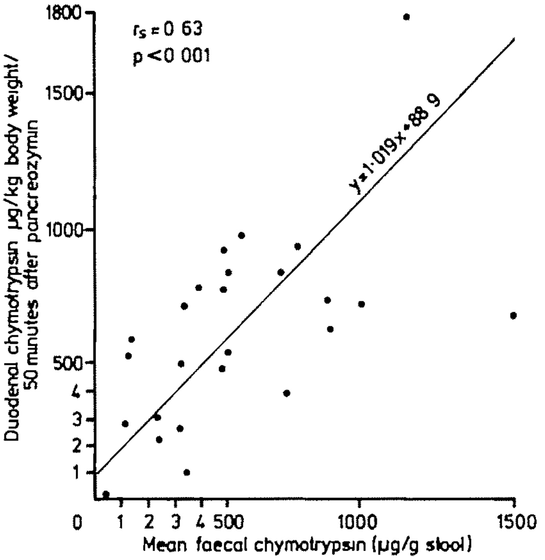

Fig 2 *Correlation of apparent secretion rates of chymotrypsin with mean faecal chymotrypsin concentrations.*

the children produced inconsistent results from either source.

PATIENTS WITH PANCREATIC INSUFFICIENCY

In the 46 children with cystic fibrosis and clinical malabsorption faecal chymotrypsin was absent in 16, and in the remaining 30 concentrations were 60% (72 μg/g stool) or less of the lower limit of our reference range. The median concentration was 6 μg/g stool, or 5% of the lower limit of the reference range.

Discussion

In the study correlating duodenal enzyme activities and faecal concentrations, mean faecal chymotrypsin concentrations derived from three separate stool specimens collected at random within 72 hours of the intraduodenal test were highly significantly correlated with the apparent secretion rates of chymotrypsin. The correlation applied whether pancreatic function was compromised or within the physiological range, with the result that the segregation in the apparent secretion rates of chymotrypsin between normal pancreatic function and pancreatic insufficiency was reproduced identically by the mean faecal chymotrypsin concentrations. In the 46 children with cystic fibrosis and clinical evidence of malabsorption faecal chymotrypsin concentrations were without exception grossly subnormal.

Various measures of correlation have been reported in adults between: duodenal output of chymotrypsin and output in 24 hour stool collections[9]; duodenal output of trypsin and chymotrypsin concentrations in stool specimens collected at random[10], and duodenal concentration of chymotrypsin and faecal concentration.[11] None, however, correlated chymotrypsin secretion rates with chymotrypsin concentration in stool specimens collected at random—the only specimens that are readily available in infants and young children. There have been no correlation studies reported in children.

It was necessary to use multiple faecal analyses to achieve the degree of association between duodenal and faecal measurements that we have shown. Using only the results from the first of the three stool analyses for correlation produced a significantly lower degree of association. Homogeneity of chymotrypsin distribution has been claimed both within the individual stool[12] and between three stool specimens collected at random on separate days.[11] This may be what usually happens, but our experience has been that the occurrence of comparatively unrepresentative results from analysis of a single stool specimen is sufficiently frequent to make multiple analyses essential. Four of the 75 individual stool analyses in the correlation study differed by more than 50% (median value=14%) from the mean value of their relevant triplicates, and the largest deviation was 84%. Such differences are quite large enough to give rise to misinterpretation of single results at the lower limit of the reference range.

Other workers have also emphasised this point, recommending the use of two[10] or more[13] stool specimens collected at random. Moeller[13] found three of 22 faecal chymotrypsin results from nine adults with pancreatic exocrine insufficiency within their control range. By repeat testing and using mean values all false negatives were eliminated. We recommend the use of three specimens collected at random. If all three stool specimens produce chymotrypsin concentrations significantly greater than the lower limit of the reference range, pancreatic insufficiency at the time of the investigation can be excluded. This would not be true for specific lipase, co-lipase, or trypsinogen deficiencies but these conditions are extremely rare.

In the 46 children with cystic fibrosis and clinically recognised malabsorption, faecal chymotrypsin concentrations were unequivocally subnormal, and single stool specimens were sufficient to identify the gross pancreatic insufficiency characteristic of the disease. The children were selected for the present study because they had malabsorption and it was not considered ethically justifiable to confirm the degree of pancreatic insufficiency by intubation and hormone stimulation

Controversy persists over the efficiency of faecal chymotrypsin measurement as a method of assessing pancreatic function because of confusion over the function and capability of the test. The test may not detect the initial stages of insufficiency in developing disease. It cannot differentiate between normal pancreatic function and chronic pancreatitis where secretion (though invariably ultimately compromised) may initially be normal, and pancreatic carcinoma where reduced secretion (if it occurs) depends on the site and nature of the lesion. The reputation of the test has suffered because it does not resolve these 'adult' problems.

In addition to the difference in the clinical questions being asked, there may be other reasons for greater specificity in children. Mean whole gut transit times are shorter in children, the transit time of the neonate[14] being about a quarter of that of the adult.[15] The shorter transit time reduces the opportunity for bacterial[16] and enzymatic[17] degradation in transit making the test more direct and increasing its specificity. Reducing adult whole gut transit time with purgatives to about that of the neonate improves the duodenal faecal chymotrypsin correlation.[9]

In addition to the high sensitivity and specificity, assessing pancreatic function by faecal chymotrypsin measurements has much to recommend it in children It is completely non-invasive, does not entail oral dosing and requires little cooperation on the part of the patient, except for stool retention. The quantity of faeces needed is too small to give offence in or outside the laboratory or to present the latter with problems of microbiological containment of potentially hazardous material. The procedure is simple, cheap, and rapid compared with other methods of measuring pancreatic function. These features make the test repeatable as often as necessary so that confirmation by repeat testing is always possible and longitudinal studies requiring frequent repeat tests are also possible.

A further advantage of chymotrypsin is its stability at ambient temperatures in the United Kingdom. Little loss of activity occurs after it has been standing at 18°C for 72 hours, so that specimens may be sent by post with confidence and without any special provision other than secure packing and avoiding weekends.

Intraduodenal testing will continue to be necessary to identify the rare, specific deficiencies of pancreatic enzymes, but in most children in whom pancreatic exocrine functions is questioned the answer should be sought first by measuring faecal chymotrypsin concentrations.

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Congenital hypothyroidism: increased incidence in Asian families

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SUMMARY Screening in the North West health region of England showed a significantly higher incidence of congenital hypothyroidism in Asian families—1/918 compared with 1/3391 in non-Asians. This could only in part be explained by consanguinity. No differences were found in birth order, season of birth, gestational age, or birth weight between normal infants and those with congenital hypothyroidism. There was a significantly higher incidence of additional congenital abnormalities (9%) and a significantly increased mortality (5%) in infants with congenital hypothyroidism compared with unaffected infants.

Since the introduction of routine screening of the newborn for congenital hypothyroidism over the past 10 years, the incidence has proved to be considerably higher than previously realised at about 1/3500 to 1/3800.[1 2] It is even more common in preterm infants [3] In addition, there has been speculation about ethnic differences in incidence,[4] season of birth,[5] increased morbidity and mortality,[6] an increase in associated congenital abnormalities including chromosomal abnormalities[7] (which is disputed[9]) that may delay the start of treatment,[6] and the presence of a thyroid growth limiting antibody in the mothers of infants with congenital hypothyroidism.[10]

In the North West health region of England 100 cases of congenital hypothyroidism have now been detected and they have been reviewed to see if the features listed were present.

Patients and methods

The North West health region had a population of 3 963 000 in 1985, which included a sizeable, mainly Moslem, Asian community. Screening for hypothyroidism by radioimmunoassay of thyroid stimulating hormone (TSH) was introduced in five health districts in November 1981, and the entire region was being screened by December 1982 One hundred cases of congenital hypothyroidism had been diagnosed in February 1987.

A blood spot from a heel prick is collected on to filter paper at the same time that the screening for phenylketonuria is done on the tenth postnatal day. A concentration of TSH of <20 mU/l is regarded as normal. If the concentration is between 20 and 40 mU/l a repeat sample is requested after checking. A concentration of >40 mU/l or a repeat value between 20 and 40 mU/l warrants formal investigation.

After a full history has been taken and examination carried out, the following investigations are done: measurement of serum concentrations of thyroxine, tri-iodothyronine, TSH, and thyroid autoantibodies in venous blood from the mother and the infant, an *x* ray to assess bone age, and a ^{99m}Tc radionuclide scan of the thyroid. If the diagnosis is confirmed treatment with thyroxine is started the same day. The local consultant paediatrician is contacted and asked to ensure follow up. The diagnosis is reviewed once at the age of 1 year when the child has not received treatment for one week after three weeks taking tri-iodothyronine. Thyroid function tests are then done to confirm permanent congenital hypothyroidism.

A few patients are not seen centrally when there are coexisting problems such as prematurity or other congenital abnormalities that require treatment elsewhere. Instead a full history is obtained by telephone where possible

Population data were derived from three sources—firstly, the district birth returns that are collated at regional headquarters to allow for the differing periods each district has had screening for congenital hypothyroidism were studied This permitted analysis by district, year of birth, sex, birth weight, gestation, and pregnancy number of all infants born in the region who survived the first 7 days of life and were thus eligible for screening. In addition, over the same time period deaths from the age of 1 week to 1 year were also obtained.

Secondly, the number of Asian births was calculated from the birth registration returns for the region sent to the Office of Population Censuses and Surveys (OPCS) based on the mother's country of birth. This excluded mothers of Asian extraction born in the United Kingdom. There was little reliable official information relating to the racial origins of the United Kingdom population or whether a marriage was consanguineous.

Thirdly, the season of birth for the normal population was based on the 2 526 000 births in England and Wales during 1980 to 1984.[11]

Statistical analysis was by the Kolmogorov-Smirnov test for goodness of fit[12] and the χ^2 test, Fisher's exact test, and Poisson distribution as appropriate.

Results

From November 1981 to February 1987, 289 697 infants (51·6% of whom were boys) survived the first 7 days of life; 18 366 (6·3%) had mothers born in India, Pakistan, or Bangladesh (henceforward referred to as Asian). Congenital hypothyroidism was diagnosed in 100 patients of whom 77 were white, 20 were Asian, one was Arab, one was Jewish, and one was Chinese, but none was black There was consanguinity in 11 Asian families, one Arab family, and one white family. The characteristics of the 100 infants with congenital hypothyroidism are shown in table 1 The incidence of congenital hypothyroidism in the region is shown in table 2. The difference in incidence between Asians and non-Asians is highly significant ($p<0·001$). The overall incidence (1/2897) is 1·3 times greater than the average in Europe (1/3800, $p<0·01$).[2] This excess is accounted for by the high incidence among Asians. The difference in the sex ratio between Asian and non-Asian (almost exclusively white) is not significant. One child with congenital hypothyroidism and multiple other congenital abnormalities was not screened (by oversight) and was diagnosed at the age of 3 months in another region.

Table 1 *Characteristics of 100 infants with congenital hypothyroidism*

Sex ratio (Male·Female)	1 2·7
Median (range) birth weight (g)	3365 (910–4760)
Gestational age (weeks)	
<37	9
37–40	44
>40	44
unknown	3
Median (range) time interval from birth to screen result (days)	16 (12–68)*
Median (range) time interval from birth to treatment (days)	19 (4–63)*

*One died before treatment started and three were treated before confirmation by screening

Table 2 *Incidence of hypothyroidism in the North West region*

Race	*Incidence*	*95% Confidence intervals*	*Male·female ratio*
Asian	1/198	1/612 to 1/1670	1 5·7
Non-Asian	1/3391	1/2740 to 1/4396	1 2 3
Total	1/2897	1/2394 to 1/3621	1 2 7

There was no evidence of an abnormal seasonal variation in births of infants with congenital hypothyroidism. In the four quarters of the year, 25·6%, 19·5%, 28·0%, and 26·8% of infants with congenital hypothyroidism were born compared with 24·4%, 25·2%, 26 0%, and 24·4% for the normal population.

There was no difference in gestational age or birth weight of infants with congenital hypothyroidism and other infants in the region: 9·2% of infants with congenital hypothyroidism and 6·4% of other infants were born before 37 weeks' gestation, and 12·7% of infants with congenital hypothyroidism and 7·1% of other infants had median birth weights of under 2500 g.

There was no difference in the order of birth of infants with congenital hypothyroidism compared with others in the region.

Thirteen couples were identified as definitely consanguineous. The infants of consanguineous couples were 4·3 times more likely to have an anatomically normal or enlarged but normally placed thyroid gland on scan than the rest of the group ($p<0·03$), but the overall incidence of findings on radionuclide scans of the thyroid was similar to that found in Europe (tables 3 and 4).[12]

Nine infants had the following congenital abnormalities. trisomy 21 ($n=2$), multicystic kidneys, bilateral hydronephrosis, pelviureteric obstruction, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, pneumothorax, cleft palate, talipes equinovarus, and spastic diplegia Two others had hyaline membrane disease. There was a high incidence of infants with trisomy 21—1/50—compared with the national incidence of 1/600 ($p<0·01$).[13]

These 11 infants were screened later than infants without additional problems. Five (45%) were screened by 20 days or older, compared with 19% of

Table 3 *Appearance of radionuclide scan*

	All families	*Asian families*	*Consanguineous families*
Aplastic	36	5	3
Hypoplastic	3	1	0
Ectopic	39	5	5
Normal	6	2	2
Enlarged, normal position	6	2	2
Unknown	10	3	0
Total	100	20	13

Table 4 *Association between scan type and consanguinity*

Consanguinity	*Appearance of scan*	
	Enlarged or normal	*Aplastic, hypoplastic, or ectopic*
Present	5	8
Absent	5	52
Total*	10	60

*All infants whose parents' marital state was known and who had a scan

Table 5 *Causes of death in infants with congenital hypothyroidism*

Cause	*Sex*	*Age at death*
Fibrosing alveolitis	Female	3 years
Possible acute adrenal insufficiency	Female	6 weeks
Extreme prematurity	Female	4 weeks
Cytomegalovirus pneumonia	Female	5 weeks
Sudden unexpected death	Male	9 weeks
Down's syndrome and prematurity	Male	13 weeks

the uncomplicated group ($p=0\cdot07$), but they did not start treatment later than the group without complications, as all those with additional problems who were still alive were treated by 29 days of age compared with 90% of the group without complications. This compares favourably with a mean time to start of treatment of 32·4 days (range 8–108) for the group with complications described by Fernhoff *et al*[5]

During the period November 1981 to February 1987, 1234 infants (0·46%) died aged 1 week to 1 year in the North West region (allowing for the differing screening periods for each district). Five (5%) of infants with congenital hypothyroidism died before the age of 1 year and one died at the age of 3 (table 5). This excess in mortality is significant ($p<0\cdot001$).

Discussion

Screening for congenital hypothyroidism in the North West health region is done comparatively late compared with other areas of the world[6] in order to coincide with the phenylketonuria screening,[10] which was established with a single community agency (health visitors) collecting the specimens on the tenth day of life. Less than 2% of infants are screened while still in hospital. The late timing of the screen may partly account for the lower detected incidence of transient hypothyroidism, which is 1/289 697 in this region compared with a reported incidence as high as 1/8000 in Europe.[1] The potential disadvantage of late screening is that infants with congenital hypothyroidism may then start their treatment late. Fernhoff[6] in Georgia, United States, screened infants between 2 and 7 days old and the mean date of starting treatment was 19 days (range 2–55) in a group without complications, compared with the median in the present study of 19 days (range 2–63, including the group with complications), suggesting little effective delay.

The results suggest that the children of Asian families are at greater risk of congenital hypothyroidism than the rest of the population. The total number of Asian births, however, does not include those mothers of Asian origin born in the United Kingdom as this information is not available. Nevertheless, the total number of identified Asian births would need to be doubled for the difference to lose its significance, and such under-reporting is most unlikely. It is not clear from the results why the Asian population has a high incidence of congenital hypothyroidism. An enlarged or normally placed thyroid on scanning was more common in families with consanguinity, but although 55% of Asian infants with congenital hypothyroidism were of consanguineous origin, less than half of the infants of consanguineous marriages had normally situated thyroids.

This suggests that currently recognised recessively inherited enzyme abnormalities do not account for the entire incidence in Asian families. If all consanguineous families are removed from the calculations the incidence in Asian families becomes similar to that in the white population. It would be interesting to know the incidence of congenital hypothyroidism in the Hindu or Sikh populations where consanguineous marriages are less common.

The suggestion that there is a maternal antibody blocking fetal thyroid genesis induced by TSH[10] in mothers of infants with congenital hypothyroidism with or without aplastic thyroids[14] prompted us to review the birth order. Van der Gaag *et al*[10] suggested that thyroid growth blockers may arise not due to autoimmunisation but because of the presence of the fetoplacental unit. If (in the manner of Rh haemolytic disease) increasing numbers of pregnancies increase the potential for appreciable sensitisation, then infants with congenital hypothyroidism ought to have a higher birth order number than the rest of the population The close similarity in the birth order of infants with congenital hypothyroidism and the general population, however, does not support this hypothesis.

Miyai *et al*[5] found an increased incidence of congenital hypothyroidism in babies born during the summer months; we did not confirm this, the summer incidence being similar to that in autumn and winter

These results confirm the higher mortality and morbidity noted previously,[6–8] especially the high incidence among infants with Down's syndrome.[15] It is essential that screening of these infants for hypothyroidism (when they are often still in hospital and not being fed on the tenth day, and thus perhaps not being screened for phenylketonuria either) is not overlooked, as a delay in treatment in this group may be even more crucial [2]

We thank David Phoenix-Stone of the department of statistical information, North West Regional Health Authority, Alan Newbigging of the OPCS, the technical staff of the North West regional hypothyroid screening laboratory, and consultant paediatric colleagues of the North West health region

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Dietary variation in diabetics

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SUMMARY The day to day variation in the energy and carbohydrate intake of 168 children with diabetes on Tyneside and Teesside was less than that of 405 non-diabetic children. It was, however, still considerable, the average range of carbohydrate intake over three days being 51 g. The variation in carbohydrate intake was not related to diabetic control nor to the families' knowledge of diabetes. Compliance with the dietary prescription deteriorated during the day. These findings support a qualitative approach to the dietary prescriptions for diabetics.

Regulation of diet is an important aspect of the management of insulin dependent diabetes mellitus. The dietary prescription entails regulating the amount and type of carbohydrate consumed which is distributed to match the action of the insulins injected. The essence of this regimen therefore is a carbohydrate intake that is constant from day to day in both total amount and distribution, extra carbohydrate being allowed only before strenuous exercise.

We report the extent of the day to day variation in the carbohydrate and energy intakes of children with diabetes and its relation to their knowledge about, and control of, their disorder.

Subjects and methods

Between July 1983 and March 1984 children attending diabetic clinics on Tyneside and Teesside were invited to record their intakes of all foods and drinks for three consecutive days. This was done in a diary, kept by parent or child as appropriate, in which the time of consumption was recorded together with a description of what was consumed, and the amount in household measures. At an interview on the fourth day this information was discussed to enhance completeness and detail. The household estimates were converted to estimates of weight of each item recorded using a variety of visual aids.[1] Computerised food tables were used to calculate the intake of energy and carbohydrate for each day.[2] Each day's intake was allocated to six arbitrary periods corresponding to the prescribed distribution—that is, breakfast, midmorning snack, lunch, midafternoon snack, evening meal, and supper snack. The day to day or within subject variation in carbohydrate and energy intakes were calculated for each subject as the standard deviation of the intake for the three days; this was also expressed as the coefficient of variation, calculated as standard deviation/mean×100. In addition, the range in carbohydrate and energy intake was calculated for each subject as the difference between the highest and lowest intakes of the three days. The difference between each subject's mean carbohydrate intake and their prescribed carbohydrate intake, which represented their compliance with diet, was also calculated.

A structured questionnaire was used to obtain social information, and a single random blood sample taken for measurement of C peptide and glycated haemoglobin A1 concentrations as measures of control. The parent(s), and child if old enough, also completed a multiple choice questionnaire to assess their knowledge about diabetes.[3]

Similar data about the diets of 405 non-diabetic children aged 11–12 (193 boys and 212 girls) in South Northumberland were used for comparison. These children had completed a two year longitudinal study of the relation between diet and dental caries that entailed recording intake in a similar way to that described for the diabetic children but on five occasions, each lasting three days. Calculations were made using identical methods from only the first of the five dietary diaries.[4] The middle age group of diabetics was chosen to be comparable to the age range of the non-diabetics.

All families were classified into socioeconomic groups according to the fathers' present or last known occupation, unemployment was recorded separately. The socioeconomic groups were divided into 4; 1 indicated professional and managerial people, 2 clerical and craftsmen, 3 semi- and unskilled labourers, and 4 those whose occupation was unknown or unclassifiable, or who had retired.

Associations among variables were examined by

Table 1 *Mean energy and carbohydrate intake and some measures of within subject variation in diabetic children*

	Total No (n=168)	*Age group (years)*		
		<10·5 (n=68)	*10·5–12·5 (n=36)*	*>12·5 (n=64)*
Mean intake of energy (MJ)	8·65	7·58	8·97	9·62
Within subject variation				
Standard deviation	1·09	0·82	1·09	1·38
Coefficient of variation (%)	13	11	12	14
Range	2·08	1·56	2·07	2·63
Mean intake of carbohydrate (g)	229	200	244	252
Within subject variation				
Standard deviation	27	19	30	33
Coefficient of variation (%)	12	10	12	13
Range	51	36	57	64

calculating Pearson's r correlation coefficients, and where confounding factors were indicated partial correlation coefficients were calculated. *t*-Tests or one way analysis of variance, including Scheffe's test for multiple comparisons, were used to calculate the significance of differences. All analyses were performed using the Statistical Package for the Social Sciences.[5]

Results

Of the 234 children attending the clinics 170 agreed to take part in the study and 168 (98 boys and 70 girls) completed dietary records Their mean (SD) age was 11·0 (3·35) years and they had been diabetic for 4·0 (2·85) years Their mean glycated haemoglobin concentration was 10·6 (2·33)% but only 150 had estimations of both glycated haemoglobin concentration and C peptide. Seventy families were classified into socioeconomic group 1, 68 into group 2, 19 into group 3, and 11 into group 4.

Table 2 *Mean intake of energy and carbohydrate and within subject variation in 405 non-diabetic children calculated from the Northumberland study*

	Energy (MJ)	*Carbohydrate (g)*
Mean intake	8·48	261
Within subject variation		
Standard deviation	1·63	53
Coefficient of variation (%)	19	20
Range	3·09	100

Table 1 shows the mean energy and carbohydrate intakes for the subjects as a group and subdivided by age. There were no significant differences in intake between the sexes or the socioeconomic groups except that the mean energy intake in social group 4 was greater than that of group 1 (10·2 and 8·3 MJ, respectively, $p<0·05$) and the carbohydrate intake of group 4 (280 g) was greater than that of the other groups (groups 1–3: 224, 230, and 219 g, respectively, $p<0·05$).

There were no significant differences in the day to day, or within subject variations in intakes, expressed as the mean coefficient of variation or as the

Table 3 *Mean intake of energy and carbohydrate and some measures of within subject variation according to time of day*

	Breakfast	*Mid-morning*	*Lunch*	*Mid-afternoon*	*Evening meal*	*Supper*
Mean intake of energy (MJ)	1·46	0·69	2·23	0·76	2·46	1·17
Within subject variation						
Standard deviation	0·32	0·30	0·59	0·41	0·84	0·50
Coefficient of variation (%)	22	44	26	54	34	43
Range	0·66	0·62	1·10	0·80	1·61	0·98
Mean intake of carbohydrate (g)	43	20	57	22	59	32
Within subject variation						
Standard deviation	8	8	15	11	19	13
Coefficient of variation	19	40	26	50	32	30
Range	17	15	29	21	37	25
Prescribed amount (g)	39	17	47	18	45	24
Difference between intake and prescription* (%)	11	17	22	27	34	37

mean range of intake over the three days, either between the sexes or the social classes ($p>0{\cdot}05$ in both cases). The carbohydrate intake of the youngest children, however, varied less from day to day than that of the other age groups ($p<0{\cdot}05$). The mean range in carbohydrate intake from day to day was 51 g for all subjects, 36 g for the youngest group, and 64 g for the oldest.

Table 2 gives similar information about the 405 non-diabetic children and shows that the within subject variations of energy and carbohydrate intakes were greater than for the diabetic children of similar age

Table 3 shows average estimates of the day to day or within subject variations in energy and carbohydrate intakes related to the prescribed meal pattern. The mean within subject coefficient of variation and the mean range of energy and carbohydrate intake are wide at each specified time. The mean within subject range of energy intake for the three day period varied from 0·6 MJ at the midmorning snack to 1·5 MJ at the evening meal, and that of the carbohydrate intake varied from 15 g at the midmorning snack to 37 g at the evening meal. The intake of carbohydrate was always greater than the prescription and the difference increased considerably as the day wore on.

There was a significant but low positive partial correlation between glycated haemoglobin concentration and the within subject coefficient of variation for energy but not for that of carbohydrate even after allowing for the effects of mean energy intake, age, and C peptide concentration (table 4). Only the variation in the energy intake at the evening meal correlated with glycated haemoglobin concentration after allowing for C peptide concentration, age, mean energy intake at that meal, and the variation in carbohydrate intake at that meal. The variation in the energy intake at the evening meal appeared to be responsible for the apparent correlation between glycated haemoglobin concentration and the variation in carbohydrate intake at the evening meal. No significant correlations were found among mothers', fathers', or children's knowledge about diabetes, or the within subject variation in energy or carbohydrate intake.

Discussion

There was wide within subject or day to day variation in the energy and carbohydrate intake of the children with diabetes. Errors in the dietary survey method may account for some of the variation. Patients are, however, likely to make errors of a similar type and degree each day when estimating the sizes of portions if food is not weighed. The intake of the children during such a study was probably closer to their dietary prescription than usual. The true variation in the intake of diabetics is therefore unlikely to be less than that reported here.

The within subject variation of both energy and carbohydrate was least in the younger children. This may indicate the extra influence of their parents who were perhaps more successful in restricting intake, or they may have reported only that intake observed or approved by them. The within subject variation in intake, however, was most impressive and ends the notion that the dietary intake of diabetics is

Table 4 *Partial correlation coefficients among some measures of day to day or within subject variation in dietary intake and glycated haemoglobin concentrations controlled for C peptide concentrations, age, and intake*

Variables		*Controlling:* *third order* *C peptide + age +*		*Fourth order* *C peptide + age +*
Dependent variable glycated haemoglobin with:				
Independent variable				
Energy Standard deviation	by	Mean daily energy +0·19 $p<0{\cdot}05$		
Carbohydrate Standard deviation	by	Mean daily carbohydrate +0·02 $p>0{\cdot}05$		
Evening meal energy Standard deviation	by	Evening meal energy +0·25 $p<0{\cdot}01$	or by	Evening meal energy + carbohydrate SD +0·21 $p<0{\cdot}05$
Evening meal carbohydrate Standard deviation	by	Evening meal carbohydrate −0·23 $p<0{\cdot}01$	or by	Evening meal carbohydrate + evening meal energy SD −0·06 $p>0{\cdot}05$

constant from day to day. Compliance, defined as the difference between intake and prescription, also was generally poor and deteriorated during the day. Nevertheless the day to day variation was less than that of the non-diabetic children and the proportion of the carbohydrate consumed at each meal or snack was similar to that prescribed. These findings, together with previously reported differences in the composition of the diet of these diabetic children compared with that of non-diabetics,[6] indicate the considerable efforts made to comply with dietary instructions.

Henry *et al* reported large variations in the intakes of 16 adult diabetics and concluded that adherence to a controlled carbohydrate diet was a fallacy [7] In reply, Black pointed out that their carbohydrate intakes were lower, and the variation less, than those seen in other population groups.[8] The results of our survey support both views; a constant carbohydrate diet was certainly a fallacy, but considerable regulation was apparent. Reports of poor adherence to dietary prescriptions are widespread[9–12] and perhaps should be considered normal.[13] There are, however, two components to adherence a mean intake that is close to the diet prescription (defined as compliance in this paper) and low day to day within subject variation. The importance of these two aspects is not clear. Although among our patients those who complied most strictly with their diets were better controlled,[6] this may have been coincidental Observational studies cannot determine cause and effect and there does not appear to have been a controlled trial of truly free diet for diabetic children.

This study showed that there was no association between glycaemic control based on a single estimate of glycated haemoglobin concentration and variation in carbohydrate intake. There was, however, a weak association between control and the variation in energy intake, which suggests that there may be some benefit in the regulation of food intake. The association between control and the variation in energy intake at the evening meal may have arisen simply because that meal was the largest and most variable. A second possibility is that intake at that time of day was not adequately covered by insulin, perhaps for fear of hypoglycaemia during the night. Further experimental studies are required to investigate these points in detail

A fundamental fallacy of dietary regulation for diabetics is suggested by the considerable fluctuation in the day to day energy intake of non-diabetic children as reported here and elsewhere [14] This probably indicates that their energy needs, especially for activity, also vary considerably. The mean energy intake of children with diabetes is similar to that of non-diabetic children[6] and there is no reason to expect that the day to day variation in their activity is different from that of non-diabetic children. Furthermore, even under laboratory conditions the effect of food intake on blood glucose in the same subject may vary greatly both with different foods with the same content of carbohydrate or even with the same food on different occasions.[15] [16] Such considerations suggest that even a monotonous diet and a restricted lifestyle would not prevent large variations in blood glucose concentration.

These results support the idea that dietary advice for diabetics should be qualitative or at most semiquantitative. Detailed suggestions for achieving this have been made elsewhere.[17] The only way to reduce the day to day variability in intake further would be to restrict the choice of foods to those of stable, known composition, to weigh or to measure all food accurately in some other way, and to limit activity. Clearly none of these is acceptable in the light of the questionable benefits. We would advocate the alternative, which is to allow free comsumption of high carbohydrate, preferably high fibre, foods at relatively constant meal and snack times together with a flexible insulin regimen, in return for regular monitoring of the effects.

The results of this study show that despite considerable efforts to comply with the comprehensive dietary instructions given, children with diabetes do not follow a constant diet. We suggest that this is inevitable if children with diabetes are to be as active as their peers. Although it is feasible for children with diabetes to alter the type of food consumed, and to some extent its distribution, the quantity is determined by the child's appetite.

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Mineral accretion in the human fetus

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SUMMARY Bone mineral content of the mid forearm was measured by photon absorptiometry in 73 white singletons (36 boys, 37 girls) born between 18 and 43 weeks' gestation. Results obtained within two weeks of birth for liveborn infants were used to establish bone mineral deposition curves approximating normal in utero development. Results for stillborn infants indicated a retardation of bone mineralisation relative to liveborn infants. This has important implications concerning previous estimates of daily calcium needs for preterm infants.

Eleven liveborn Asian singletons and nine pairs of white twins were examined similarly. With respect to bone mineral content, weight, and crown-heel length, Asians with gestational ages over 35 weeks and twins were closely comparable with their white singleton peers. Asians under 35 weeks tended to be smaller than white singletons of comparable age.

Single photon absorptiometry has become an important technique for the investigation of disorders of skeletal mineralisation in the newborn.[1-3] It has been shown to be an accurate and reproducible measure of bone mineral content in the fetus[4] and to be more sensitive in detecting bone mineral deficit in the newborn than conventional radiography.[3]

As part of a larger study of bone mineralisation in the neonate, we obtained measurements of bone mineral content and anthropometric data on fetuses and infants born between 18 and 43 weeks' gestation. The data on liveborn white infants have been taken to represent normal values for bone mineralisation in utero in relation to gestational age. These values are required as a reference against which postnatal changes in bone mineral content, measured longitudinally in individual infants, can be assessed. At any gestational age the normal rate of mineralisation in utero is most likely the optimum figure against which the success of postnatal dietary supplementation should be judged.

Daily dietary requirements for calcium and phosphorus after birth have previously been estimated from results of whole body analysis of infant cadavers, some of the infants having been stillborn.[5] At any gestational age, however, systematic differences might exist between skeletal mineral content in stillborn and liveborn infants, and hence the daily mineral requirement derived using that approach might be invalid. We therefore studied white stillborn infants and spontaneous abortions as a separate group in order to find out whether or not they are an acceptable model for estimating the postnatal mineral requirements of preterm infants.

Observations of Asian singletons and white twins have also been compared with results obtained in white singletons.

Patients and methods

Seventy three white singleton infants were studied (36 boys, 37 girls). Infants born after 28 weeks' gestation who showed extreme intrauterine growth retardation—that is, those whose weight was below the third centile on standard charts—were excluded from the study.[6] Gestational age, assessed to the nearest week by maternal dates, ranged from 18 to 43 weeks inclusive. Twelve of the boys and four of the girls were either spontaneous abortions or stillborn. (Such infants are collectively described below as 'stillborn infants'.) Causes of abortion or stillbirth were heterogeneous with the most common cause being abruptio placentae. The infants were grouped by gestational age in one week intervals, keeping liveborn and stillborn infants separate. The number in each subgroup, together with weight at birth (measured in all except four infants), is given in table 1.

Eleven liveborn Asian singletons and both members of nine white twin pairs born during the three year period of the study were also examined. In two pairs of twins both twins were stillborn. Basic

Table 1 *Mean weight at birth in white singletons grouped by gestational age Where the data are incomplete the number of infants for whom the mean was computed is given in parentheses*

Gestational age (weeks)	*Boys*		*Girls*	
	No	*Weight (g)*	*No*	*Weight (g)*
		Stillbirths		
18	1	[illegible]	—	—
19	1	171	—	—
22	2	[illegible]	—	—
23	2	405	1	379
25	—	—	2	626
26	1	505	—	—
27	1	[illegible]	—	—
28	—	—	1	1336
31	1	1520	—	—
33	1	1730	—	—
35	1	3035	—	—
39	1	3490	—	—
		Live births		
26	—	—	1	795
27	—	—	3	1147
28	2	1375	—	—
29	1	1490	2	1475
30	2	1505	2	1438
31	3	1530	6	1491
32	2	2025	5	1776
33	—	—	2	2200
34	1	2530	—	—
35	—	—	1	2760
36	—	—	1	—
38	1	3030	1	2980
39	4	3530	—	—
40	5	3905(3)	6	3510
41	—	—	2	3945
42	1	3700	1	3420
43	2	4230(1)	—	—

information on Asians and twins is given in tables 2 and 3 respectively Weight at birth was not measured in one Asian singleton.

Bone mineral content of the right mid forearm was assessed in each case by single photon absorptiometry using a scanner designed specifically for measuring infants. Informed parental consent to carry out absorptiometry was obtained for all liveborn infants. Details of the scanner and its calibration have been given in earlier publications.[3,4] The method entails measurement of the absorption of a narrow beam of monochromatic radiation as it slowly traverses the forearm. The radiation exposure is extremely small; skin entrance dose is 0·03 mGy (3 millirads) per investigation (a 0·5 cm length of the forearm is irradiated). Bone mineral content results are expressed as ash weight/unit length of the bones (mg/cm) and include the mineral content of both the ulna and radius. The scans were performed within two weeks of birth in the liveborn infants and measurements of weight and crown-heel length were taken on the day of the scan. The forearm bones of the stillborn infants were scanned under water after excision and removal of surplus soft tissue. Results of absorptiometry and weight and crown-heel length (CHL) measurements are summarised in tables 2–5.

Most of the statistical analysis is based on linear regression with gestational age at birth as the independent variable. The dependent variable was always subjected to logarithmic transformation before regression analysis. Whenever any regression equation was used to estimate the value of the dependent variable, the value of the independent variable was always within the range of the data on which the regression equation was based.

Table 2 *Observations on liveborn Asian singletons Weight was measured at birth and, when absorptiometry was performed within two weeks of birth Where the data are incomplete, the number of infants for whom that mean was computed is given in parentheses*

Gestational age (weeks)	*Sex*	*No of infants*	*At birth*	*At absorptiometry*			
			Weight (g)	*Mean time after birth (weeks)**	*Bone mineral content (mg/cm)*	*Weight (g)*	*Crown-heel length (cm)*
28	M	2	975	1·5	81·7	910	34·9
29	F	1	750	0·7	86·2	660	34·3
33	F	1	750	0·3	49·8	790	33·0
36	M	1	1970	0·6	135·1	1920	45·6
37	M	1	3040	0·1	168·9	3015	48·9
37	F	1	3030	0·6	132·0	3010	57·0
38	M	2	3345	0·5	200·5	3185	49·8
39	M	2	3030(1)	0·4	197·2	3245	51·2

*Time after birth at which measurements were performed

Table 3 *Observations on white twins For each pair individual data are given for twins I (firstborn) and II. Weight was measured at birth and in the liveborn infants again when absorptiometry was performed, within two weeks of birth*

Gestational age (weeks)	*Twin*	*Sex*	*At birth*	*At absorptiometry*			
			Weight (g)	*Mean time after birth (weeks)**	*Bone mineral content (mg/cm)*	*Weight (g)*	*Crown-heel length (cm)*
				Stillbirths			
22	I	M	369	—	29·1	—	29·0
	II	M	355	—	27·8	—	26·0
30	I	F	1700	—	89·1	—	43·0
	II	F	985	—	68·4	—	37·5
				Live births			
29	I	M	1175	0·1	73·1	1170	37·5
	II	M	1100	2·0	77·9	1100	38·6
30	I	F	1400	1·0	72·6	1220	39·2
	II	F	650	1·0	61·1	730	33·3
31	I	M	1540	1·3	96·8	1431	40·0
	II	F	1800	1·3	115·5	1725	43·1
31	I	F	1350	1·7	84·1	1350	40·0
	II	M	1400	1·7	108·9	1400	38·2
32	I	M	1400	1·4	115·6	1360	40·0
	II	M	2000	1·4	111·1	1710	42·5
32	I	M	1850	1·1	153·1	1820	42·8
	II	M	1550	1·1	131·9	1550	40·4
32	I	M	2000	0·1	127·6	2000	42·6
	II	M	1800	0·1	119·8	1850	43·2

*Time after birth at which measurements were performed

Table 4 *Mean bone mineral white content and crown-heel length in stillborn singletons*

Gestational age (weeks)	*Boys*			*Girls*		
	No	*Bone mineral content (mg/cm)*	*Crown-heel length (cm)*	*No*	*Bone mineral content (mg/cm)*	*Crown-heel length (cm)*
18	1	19·1	22·8	—	—	—
19	1	14·4	20·0	—	—	—
22	2	34·2	28·5	—	—	—
23	2	32·3	28·0	1	41·5	—
25	—	—	—	2	43·3	31·3
26	1	43·6	—	—	—	—
27	1	57·9	32·5	—	—	—
28	—	—	—	1	24·6	37·5
31	1	99·9	42·0	—	—	—
33	1	75·9	47·0	—	—	—
35	1	143·5	48·0	—	—	—
39	1	169·3	51·5	—	—	—

Results

WHITE SINGLETONS

(1) Birthweight

Mean values of weight at birth in relation to gestational age are given in table 1 and individual values are plotted against gestational age in fig 1.

Although the form of the true relation in utero between weight and gestational age is unknown, a discontinuity between the data on stillborn and liveborn infants with a change in gradient at about 30 weeks' gestational age is shown (fig 1), below 30 weeks most infants were stillborn (12 out of 21 cases) and at and above 30 weeks most were liveborn (48 out of 52 cases)

Because in this set of data there was no detectable systematic difference in birth weight between boys and girls, the data were pooled. Birth weight

Table 5 *Mean bone mineral content weight, and crown-heel length in liveborn white singletons The data are complete for all infants. In contrast with table 1, mean weight values given below were obtained from measurements taken on the day of the measurement of bone mineral content*

Gestational age (weeks)	*Boys*					*Girls*				
	No	*Mean time after birth (weeks)**	*Bone mineral content (mg/cm)*	*Weight (g)*	*Crown-heel length (cm)*	*No*	*Mean time after birth (weeks)**	*Bone mineral content (mg/cm)*	*Weight (g)*	*Crown-heel length (cm)*
26	—	—	—	—	—	1	1·7	93·0	700	32·3
27	—	—	—	—	—	3	1·1	78·7	1008	37·8
28	2	1·8	107·0	1250	38·3	—	—	—	—	—
29	1	1·4	104·4	1400	39·7	2	1·2	116·0	1475	39·3
30	2	0·4	122·5	1605	41·8	2	1·6	111·1	1305	40·9
31	3	0·7	92·5	1570	40·9	6	1·5	96·6	1362	40·8
32	2	1·5	154·5	1953	43·6	5	0·7	130·5	1786	43·4
33	—	—	—	—	—	2	0·5	167·0	2200	42·8
34	1	0·7	173·3	2600	45·8	—	—	—	—	—
35	—	—	—	—	—	1	0·6	198·3	2570	47·5
36	—	—	—	—	—	1	0·9	161·9	2580	46·6
38	1	0·6	217·5	3030	49·0	1	0·1	191·8	2980	51·0
39	4	0·5	205·1	3580	50·8	—	—	—	—	—
40	5	0·6	218·7	3754	53·5	6	0·3	198·0	3503	54·2
41	—	—	—	—	—	2	0·2	194·9	3945	57·5
42	1	0·1	206·3	3700	51·0	1	0·7	261·1	3510	51·3
43	2	0·5	229·0	4185	56·5	—	—	—	—	—

*Time after birth at which measurements were performed

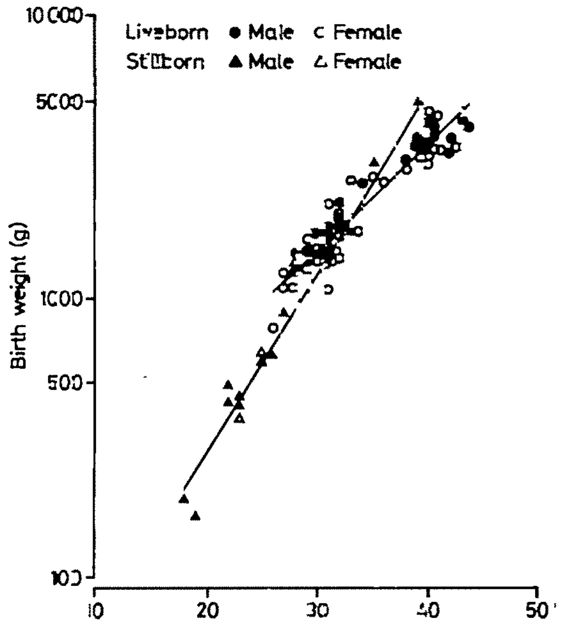

Fig 1 *Weight at birth in relation to gestational age in white singleton stillborn and liveborn infants. A log scale has been used on the y axis.*

(BWt g) can be estimated from gestational age (GA weeks) using the equations:

Stillborn infants: $\log(\mathrm{BWt})=1{\cdot}168+0{\cdot}0644\ \mathrm{GA}$
($r=0{\cdot}98$, $p<0{\cdot}001$)
Liveborn infants: $\log(\mathrm{BWt})=2{\cdot}040+0{\cdot}0379.\mathrm{GA}$
($r=0{\cdot}95$, $p<0{\cdot}001$)

Logs are to the base 10. The regression lines are shown in fig 1. The standard errors of estimate for log(BWt) are 0·0858 and 0·0652 for the stillborn and liveborn infants respectively.

(2) Anthropometric data at time of absorptiometry Absorptiometry was performed within two weeks of birth, and crown-heel length was measured on the same day The mean time since birth of the crown-heel length measurements was 0·8 weeks in the liveborn white boy singletons and 0·9 weeks in the liveborn girls. A plot of the crown-heel length measurements against gestational age is shown (fig 2). Like fig 1, it shows a change in gradient between the data on stillborn and liveborn infants.

Crown-heel length can be estimated from gestational age at birth using the equations:

Stillborn infants: $\log(\mathrm{CHL})=1{\cdot}006+0{\cdot}0193.\mathrm{GA}$
($r=0{\cdot}97$, $p<0{\cdot}001$)
Liveborn infants: $\log(\mathrm{CHL})=1{\cdot}251+0{\cdot}0118.\mathrm{GA}$
($r=0{\cdot}95$, $p<0{\cdot}001$)

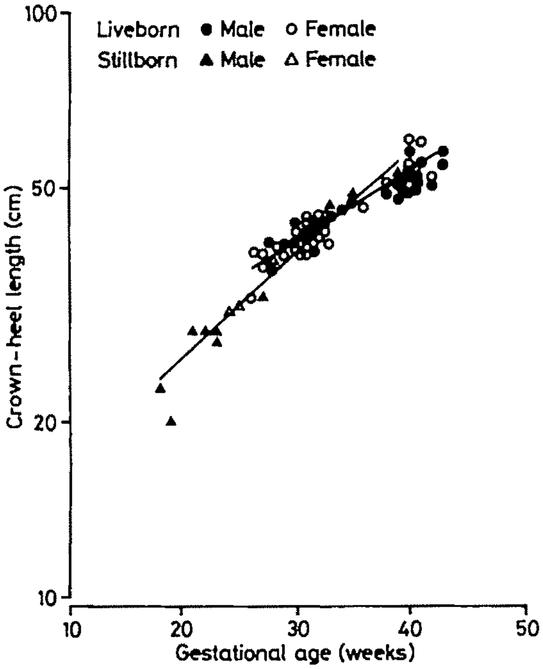

Fig 2 *Crown-heel length, measured when absorptiometry was performed, in relation to gestational age in white singleton stillborn and liveborn infants A log scale has been used on the y axis.*

The standard errors of estimate are 0·030 and 0·021 respectively. The regression lines are shown in fig 2.

In the interval between birth and absorptiometry the weight in the boys decreased on average by a mean (SE) 31·2 (13·2) g ($p<0{\cdot}05$) and in girls it decreased by 51·3 (20·9) g ($p<0{\cdot}02$). For the two sexes pooled the mean decrease in weight was 43·3 (13·6) g ($p<0{\cdot}01$).

(3) Absorptiometric data

Individual data of bone mineral content obtained within two weeks of birth are plotted against gestational age (fig 3), and separate regression lines are shown for data on stillborn and liveborn infants. Estimates of bone mineral content (BMC) (mg/cm) from gestational age (GA weeks) can be obtained using the equations:

Stillborn infants: $\log(\mathrm{BMC})=0{\cdot}437+0{\cdot}0465.\mathrm{GA}$ ($r=0{\cdot}91$, $p<0{\cdot}001$)

Liveborn infants: $\log(\mathrm{BMC})=1{\cdot}179+0{\cdot}0285.\mathrm{GA}$ ($r=0{\cdot}85$, $p<0{\cdot}001$)

The standard errors of estimate are respectively 0·126 and 0·090. The regression lines are shown in fig 3; the discontinuity between the data on stillborn

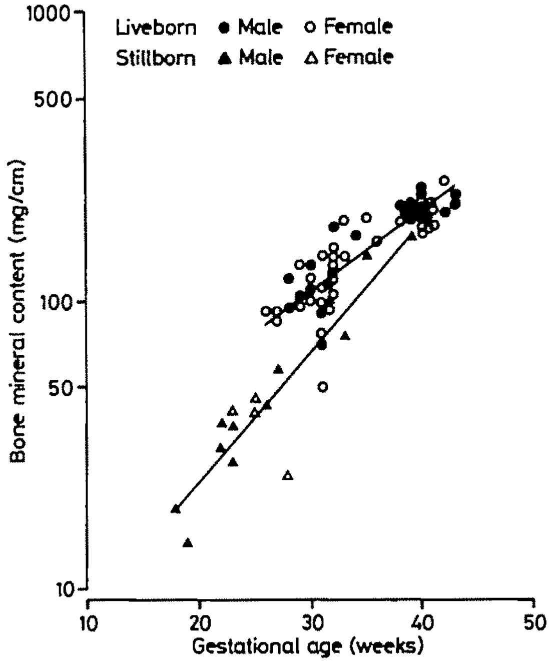

Fig 3 *Bone mineral content of the mid forearm, measured within two weeks of birth, in relation to gestational age in white singleton stillborn and liveborn infants. A log scale has been used on the y axis*

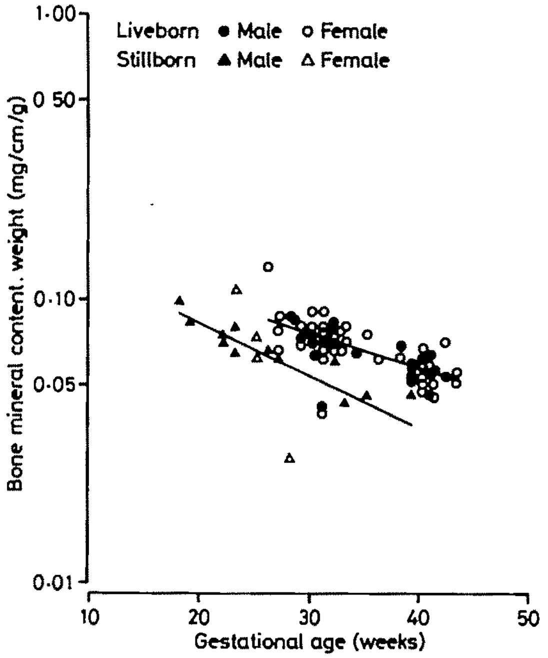

Fig 4 *Bone mineral content weight ratio in relation to gestational age in white singleton stillborn and liveborn infants. A log scale has been used on the y axis.*

and liveborn infants is clear. In contrast with the relation between weight at birth and crown-heel length with gestational age (figs 2 and 3), the discontinuity is shown as a displacement rather than a change in gradient. In the region where the stillborn and liveborn groups overlapped (around 30 weeks' gestational age), bone mineral content was substantially lower in the stillborn infants than in the liveborn infants. Using the equations of the regression lines given above to estimate bone mineral content at a gestational age of 30 weeks, the estimate for stillborn infants was 67·9 mg/cm and for liveborn infants was 108·1 mg/cm; values for bone mineral content in stillborn infants were on average 37% lower than in liveborn infants at 30 weeks' gestation.

The regression equation for liveborn infants indicated that a bone mineral content value of 88 mg/cm (midway between the two estimates quoted above) would be reached at about 27 weeks' gestation by a fetus that is subsequently prematurely liveborn. The regression line for stillborn infants indicated that this bone mineral content value would be reached at about 33 weeks' gestation (if the fetus had not already died), that is, about six weeks later than in the viable fetus.

The difference between stillborn and liveborn infants is further emphasised when individual data for the ratio bone mineral content (BMC):weight (at time of absorptiometry) are plotted against gestational age (fig 4) The data on liveborn infants indicated that bone mineral content does not increase in proportion to weight during 'normal' development in utero; there was a significant inverse correlation between log (BMC:weight) and gestational age. The data on stillborn infants were, with few exceptions, at all gestational ages lower than the data on liveborn infants; again, an inverse correlation was observed. The equations of the regression lines shown in fig 4 are:

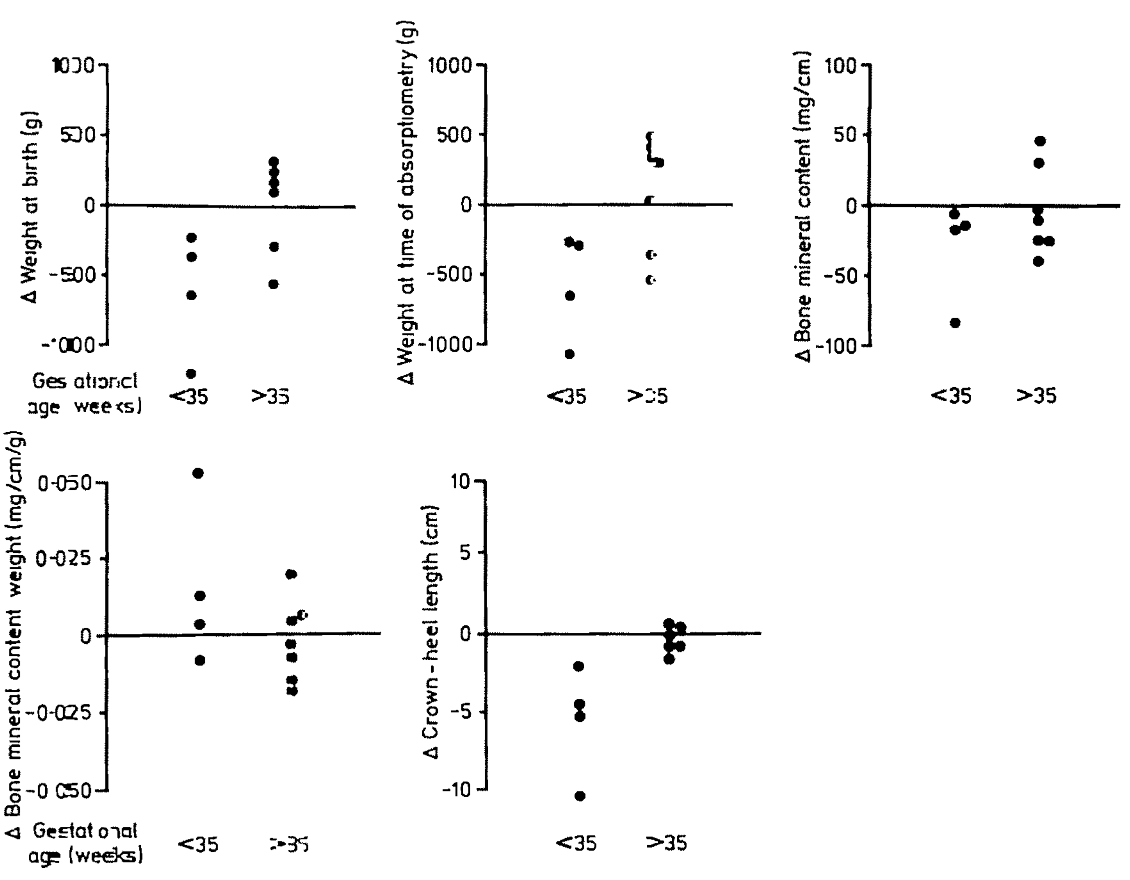

Fig 5 *Deviations (Δ) of measured values in liveborn Asian singletons from expected values in liveborn white singletons.*

Stillborn infants:

$$\log(\text{BMC:weight}) = -0{\cdot}735 - 0{\cdot}0178.\text{GA}$$
$$r = 0{\cdot}57,\ p < 0{\cdot}02)$$

Liveborn infants:

$$\log(\text{BMC:weight}) = -0{\cdot}775 - 0{\cdot}0121.\text{GA}$$
$$(r = 0{\cdot}65,\ p < 0{\cdot}001)$$

The standards errors of estimate are 0·154 and 0·071 respectively.

ASIAN SINGLETONS

Individual data on Asian singletons, split into groups below and above 35 weeks' gestational age, are shown in fig 5. The results are expressed as deviations from the appropriate regression line; a positive deviation is such that the measured value exceeds the expected value predicted by the regression equation.

Most of the infants in the group over 35 weeks' gestational age compared closely with liveborn white infants with respect to weight at birth, weight at the time of absorptiometry, bone mineral content, bone mineral content:weight, and crown-heel length. Accepting the possibility that the gestational ages might be inaccurate, liveborn Asian infants under 35 weeks' gestational age were in the main smaller in every respect than their white counterparts, although the number of cases examined was too small for statistical analysis; in all cases, body weight and bone mineral content were below the expected values for liveborn white infants. The ratio of bone mineral content:weight was close to the expected value in three out of the four cases with both measurements.

WHITE TWINS

Individual data expressed as deviations from the appropriate regression line are plotted in fig 6.

(1) Stillbirths

Results on the two pairs of stillborn white twins expressed as deviations from the regression lines for

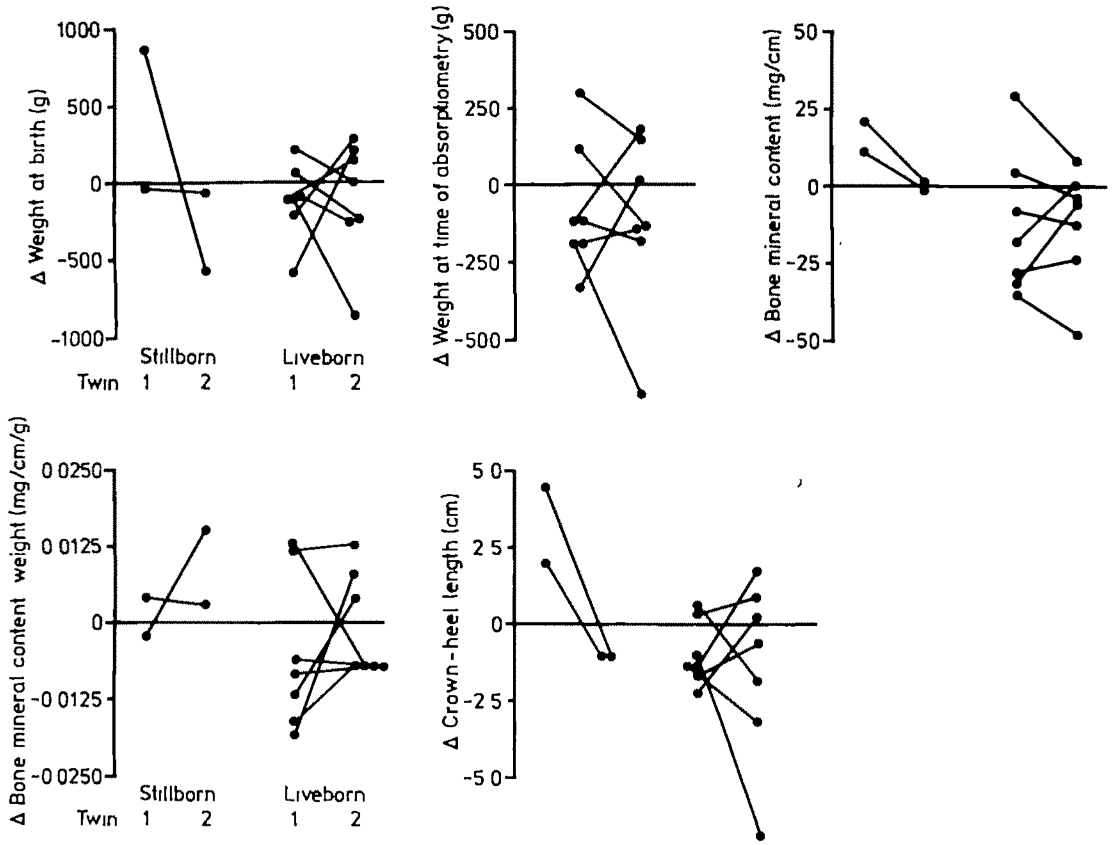

Fig 6 *Deviations (Δ) of measured values in stillborn and liveborn white twins from expected values in white singletons of similar type. Values for the first born twin are on the left for each pair*

stillborn white singletons showed no evidence of systematic bias, either positive or negative.

(2) Live births

With the exception of one second born girl twin, the measurements on liveborn white twins compared closely with expected values in liveborn white singletons with respect to body weight at birth, crown-heel length, weight at the time of absorptiometry, bone mineral content, and bone mineral content:weight. The exceptional twin (gestational age 30 weeks) had reduced body weight, crown-heel length, and bone mineral content.

Discussion

Because photon absorptiometry has been shown to be superior to radiological and biochemical methods in the diagnosis of osteopenia of prematurity[3] it is important to establish a 'normal' intrauterine mineral accretion curve as an adjunct to the investigation and treatment of infants at risk of developing postnatal osteopenia. The above results, obtained as part of a larger series of investigations of bone mineralisation in the neonate, provide the required reference values together with standard anthropometric data in the same individuals.

In this study the relation between birth weight and gestational age for liveborn white infants was found to be exponential (fig 1). A similar relation in a larger series has previously been reported by Shaw.[7] Comparison of the relations between birth weight and gestational age for stillborn and liveborn white infants, however, showed a disparity in our data. At comparable gestational ages, stillborn infants tended to have lower birth weights than liveborn infants. Observations of crown-heel length, reduced in stillborn compared with liveborn infants, provided corroborative evidence of intrauterine growth retardation (fig 2).

Also with respect to body weight, our data indicated as expected a loss between birth and the time at which absorptiometry was performed (less than two weeks after birth). Weight loss in the first week of life is usual.

In liveborn white infants born between 26 and 43 weeks' gestation the relation between bone mineral content in the forearm and gestational age was found to be curvilinear and was fitted to an exponential function (fig 3). Greer *et al* also found a curvilinear function to provide a better fit to similar data than a linear function.[8] Over smaller gestational age ranges, however, the relation can appear to be linear.[2] It is possible that bone mineralisation in reality follows different types of growth curve at different sites in the skeleton. For example, Vyhmeister *et al* measured bone mineral content at the midshaft of the humerus in 148 infants between 26 and 42 weeks' gestation, and concluded that their data could be described equally well by linear or curvilinear functions.[9] Although the shapes of growth curves obtained from different sources might differ in detail, the point is illustrated (fig 7) that the relative magnitudes of the changes in mineralisation observed between gestational ages of 24 and 40 weeks are comparable, particularly over 28 weeks' gestation. Like our data for bone mineral content, anthropometric measurements increased exponentially with gestational age as did those reviewed by Shaw.[7]

Because almost all the body's calcium is found in the skeleton, total body calcium content provides an alternative to local bone mineral content as a measure of general skeletal mineralisation. In his analysis of selected data from the literature, Shaw found an exponential relation between fetal total body calcium content and gestational age.[10] Similarly, Forbes examined data for total body calcium content from five other sources and came to the same conclusion.[11] Ziegler *et al* analysed a further set of data, fitted modified exponential functions to several growth related variables, and presented

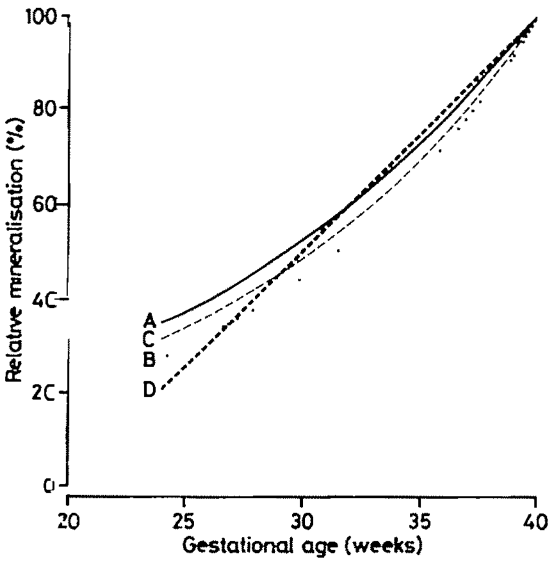

Fig 7 *Comparison of bone mineralisation growth curves from three sources, all normalised to 100% at the gestational age of 40 weeks. (A) Curve for the mid-forearm presented in this paper, (B) curve for the forearm (distal one third) published by Minton et al[2]; (C) curve for the humerus published by Vyhmeister et al[9]; (D) straight line fitted by Vyhmeister et al to the same data as curve (C)*[9]

tables of values of the variables in relation to gestational age.[12] The results of the above mentioned studies were reasonably consistent, with the total body calcium content in a full term infant being about 30 g. At 24 weeks' gestation total body calcium content was found to be only 10–15% of its value at full term.

In contrast, bone mineral content (in the forearm) has by that stage reached about 35% of its full term value. Thus although at any particular value of gestational age it is still possible that in a group of infants bone mineral content is linearly related to total body calcium content, it seems unlikely that the equation of such a line is independent of gestational age. It might therefore be dangerous to regard a change in bone mineral content (observed over a span of gestational ages) as an estimator of change in total body calcium content. This reservation is, however, based on measurements of total body calcium content in groups including stillborn infants which, as we have shown, are likely to have undermineralised bones.

Our measurements of bone mineral content in stillborn infants were consistently lower than the values predicted from the relation between bone mineral content and gestational age observed in liveborn infants (figs 3 and 4). A regression equation was evaluated for the stillborn group, but it should not be taken to describe the way bone mineral content changed with gestational age in the individual infants before being stillborn. Although the possibility of demineralisation after death cannot be excluded, this line is more likely to be the result of observing a heterogeneous group of infants in which individuals fell progressively further below the 'normal' curve as they grew. If that interpretation is correct, each individual result might be a direct manifestation of a general disorder of calcium metabolism in utero and it is possible that such a condition might be a factor contributing to the risk of stillbirth.

It has already been noted above that stillborn infants are relatively short in stature, and on that basis it might seem reasonable to have taken crown-heel length into account when comparing stillborn with liveborn infants. Crown-heel length, however, is dependent on the size of the skeleton, as is bone mineral content, and there is a continuous relation in utero between the two variables in infants subsequently liveborn. We think it is likely that in infants subsequently stillborn the relation might be the same—that is, that the skeletal mineralisation defect associated with stillbirth affects both crown-heel length and bone mineral content. In that situation, the only way the defect can be detected is by examining the measurements of bone mineral content in relation to gestational age alone, and we therefore chose not to take crown-heel length into account when comparing the stillborn and liveborn groups.

The observation of retarded mineralisation in stillborn infants has important implications regarding daily calcium requirement in premature infants. Some authors have based their estimates of requirement on the change in total body calcium content between a given gestational age and full term,[3] but the change is calculated from measurements on infants including stillborn cases.[13 14] Consequently the daily calcium requirement of 120–130 mg/kg/day is likely to be an overestimate because data from stillborn infants in the earlier gestational age groups will bias the mean total body calcium content downwards and as a result the calculated increment in total body calcium content between birth and full term will be too large. Given the patient management problems created by dietary calcium supplementation, which might include acidosis and hypercalcaemia, any reduction in calcium intake that remains consistent with the infant's true requirement is advantageous.

In an early study using the same technique we showed bone mineral content to be closely similar in full term Asian and white infants.[15] The data in this study for Asian infants born after 35 or more weeks' gestation were consistent with the previous conclusion. Below the gestational age the Asian infants tended to have lower values for bone mineral content and weigh less than their white counterparts; the few data available suggested that the values for bone mineral content were more appropriate to body weight than recorded gestational age.

Measurements on twins showed no mineralisation deficit relative to their singleton peers. One twin showed signs of nutritional compromise in utero, mimicking the findings in stillborn white singletons.

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Cardiac anomalies in Williams-Beuren syndrome

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SUMMARY We have described some of the cardiological findings in 66 patients with Williams-Beuren syndrome and analysed the two dimensional cross sectional echocardiograms in 61 of them in comparison with normal controls. Supravalvar aortic narrowing was shown in all patients examined echocardiographically and may be a useful diagnostic sign. We documented a 7·8% incidence of systemic hypertension, a 15% clinical and echocardiographic incidence of mitral valve prolapse, and a 11·6% incidence of bicuspid aortic valve.

Williams *et al* in 1961 reported four patients with the triad of characteristic facies, mental retardation, and supravalvar aortic stenosis.[1] Subsequently, Beuren *et al* noted the frequent association of peripheral pulmonary stenoses.[2] Although arterial stenoses have been well documented in this group of patients,[3 4] intracardiac abnormalities appear to be rare. The object of this study was to make a general clinical cardiological survey of a number of patients with Williams-Beuren syndrome, with regard to the incidence of intracardiac abnormalities and systemic hypertension and with particular reference to the incidence of supravalvar aortic stenosis using two dimensional sector scanning and pulsed Doppler studies of the aortic root. Arterial stenoses were neither documented nor examined. For the purposes of the study we did not differentiate between patients thought to have Williams-Beuren syndrome and those thought to have Fanconi type hypercalcaemia[5] as there was no good evidence to suggest a disparity in cardiac findings between the two groups.

Patients and methods

We performed a cardiological examination on a total of 66 patients (31 male, 35 female) aged 8 months to 29 years (mean 9·8 years). Twenty patients were over 16 years of age. Most of these patients were members of the Infantile Hypercalcaemia Foundation, which has been previously reported, and we made no distinction into which of the two subgroups they had been entered.[6] Their selection depended on the parents' willingness to bring their children for examination. Indeed, 18 of the volunteers were thought to have completely normal hearts. Arm and foot pulses were felt and compared and the blood pressures were measured in both arms in the sitting position by two independent observers. The systolic and diastolic pressures were plotted on centile charts[7] using the same criteria as in a previously reported series.[6] A chest radiograph was taken and 12 lead electrocardiogram recorded. Routine cross sectional echocardiographic studies were carried out using an Advanced Technology Laboratories Mark 100 and 600 echocardiograph with the latter having adaptive pulse wave Doppler facility; 3·5 MHz and 5 MHz transducers were used. Recordings were made in standard echocardiographic planes with the patient either in the supine or 30° left lateral decubitus position. Special emphasis was made on recording the high parasternal long axis view and suprasternal view in order to visualise the aortic root and ascending aorta. Measurements of the internal diameter of the aorta were made in end diastole at the aortic annulus (D1), the sinotubular junction (D2), and distal ascending aorta (D3) (fig 1). The flow patterns were studied at these sites. Identical recordings and measurements were made on 66 normal age matched controls. Anatomical clarification of aortic root abnormality was related to the previously described types—namely, hourglass or segmental, tubular hypoplasic, and membranous supravalvar diaphragm.[8] Routine pulsed Doppler flow was made with particular reference to D2 and D3.

Results

Altogether 66 patients were examined: of these seven had had previous cardiac surgery; four had had surgical relief of supravalvar aortic stenosis, one relief of pulmonary valve stenosis, one resection of thoracic coarctation of the aorta, and one closure of

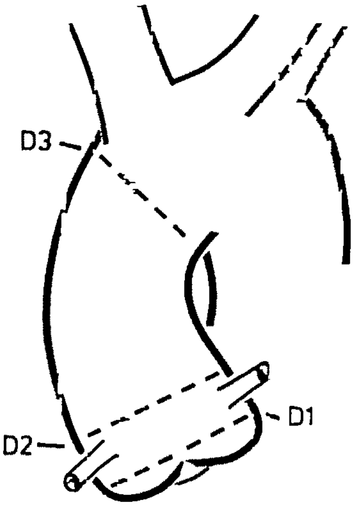


Fig 1 *Diagram of normal aortic root showing areas of measurement. D1=aortic annulus, D2=sinotubular junction; D3=distal ascending aorta*

a secundum atrial septal defect. In the particular group of children who volunteered for this study there were no patients awaiting surgery for relief of supravalvar aortic stenosis and of the seven patients who had had no surgical intervention but had been catheterised, the maximum supravalvar aortic gradient measured was 20 mm Hg. These seven patients had normal electrocardiograms, as did all the other patients who had not had surgery and had no other congenital cardiac defect In three patients there were no abnormal auscultatory findings. The other 63 patients had systolic murmurs heard bilaterally in the neck, often loudest on the right side. The intensity varied from soft to loud. Eight of these 63 patients (13%) had widespread bilateral systolic murmurs, thought to be due to peripheral pulmonary stenoses. Ten patients (16%) had clinical signs thought to be those of mild mitral incompetence with a click, murmur, or both One patient had signs indicating pulmonary valve stenosis and a small ventricular septal defect. A further patient had abdominal bruits and had a proven abdominal coarctation of the aorta

Blood pressure recordings of two observers were compared and when both were definitely taken with the patient at rest, the higher recording was tabulated. In four cases the systolic blood pressure in the right arm was greater than 20 mm above that in the left and the higher reading was charted Using the criteria of systolic and diastolic blood pressures of over the 95th centile as representing hypertension, which have been previously adopted,[6] we found five patients to be hypertensive (8%). An additional four patients had systolic hypertension. A further three patients had systolic blood pressures at the 90th centile. Of the 12 patients with blood pressures of the 90th centile and above there were nine males and three females. Five patients were over 16 years of age and seven under 16 years of age. Three of the five adult patients had had previous aortic root surgery. One of the children had had aortic root surgery and one relief of thoracic coarctation of aorta; a third had abdominal coarctation of aorta.

CROSS SECTIONAL ECHOCARDIOGRAPHY

Many of the patients were hyperactive and five of the 66 recordings could not be completely analysed. The aortic root recordings of the four patients who had had aortic root surgery were excluded from analysis of this structure. Detailed measurements of the aortic root were possible in 57 patients and pulsed Doppler studies were possible in the same number of patients.

Of the 61 recordings, nine (15%) showed mitral valve cusp prolapse—in seven cases prolapse was confined to the anterior cusp and in two both cusps were affected. A small perimembranous ventricular septal defect was shown in one patient, who also had pulmonary valve stenosis. A bicuspid aortic valve was shown in seven patients (11%). Peripheral pulmonary arterial stenoses was shown in only the two patients with proximal branch stenoses.

The 57 aortic root measurements showed a significant narrowing at the sinotubular junction as compared with the aortic annulus ($p<0 \cdot 001$) in the patients as compared with the aged matched controls. The internal and diastolic measurements of aortic annulus (D1) in the patients was from 11 mm to 21 mm and the same measured in the control series was between 10 mm and 24 mm (fig 1). Measurement of the sinotubular junction (D2) was recorded between 7 mm and 18 mm in the patients and between 12 mm and 24 mm in the controls (fig 2). The ratio of these two measurements varied between 57% and 90% in the patients and 90% and 120% in the controls (fig 2). In all the patients the measurement of D2 was less than D1 but in none of the controls. In 15 patients the sinuses of Valsalva appeared definitely abnormal. Two categories of aortic root abnormality were detected, namely an hourglass constriction in 51 patients (fig 3) and tubular hypoplasia in six patients.

Pulsed Doppler studies showed dispersion of laminar flow in 48 out of 57 cases at D2 and D3 level (fig 4). Significant flow turbulence was noted in all cases in which the D1.D2 ratio was 70% and less. The measured narrowing at the sinotubular junction and abnormal flow patterns varied with the intensity

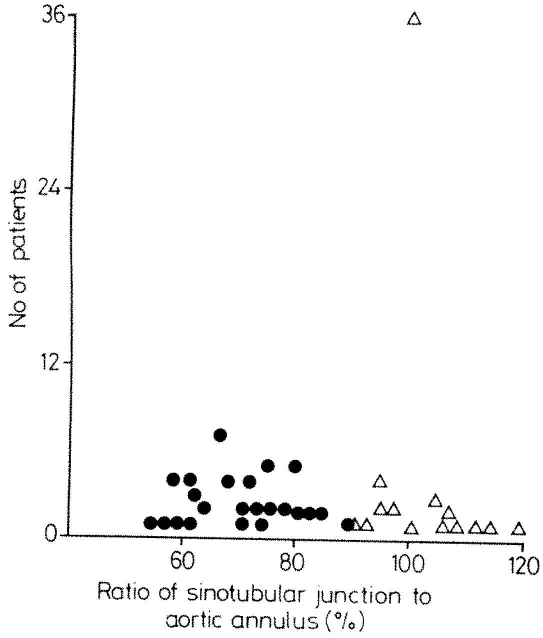
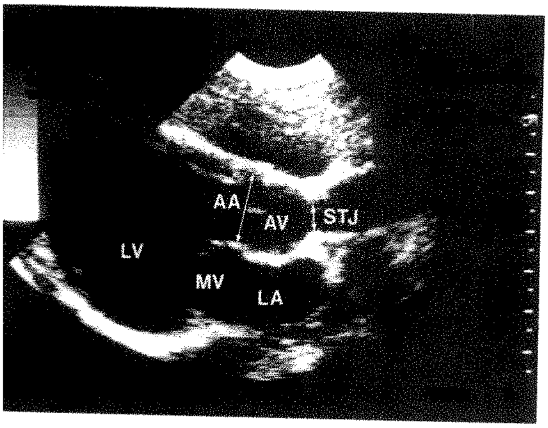


Fig 2 *Graph plotting ratio of sinotubular junction to aortic annulus (D2:D1). Patients=●; controls=△.*



ig 3 *Two dimensional scan. Parasternal long axis view of atient with hourglass type of supravalvar aortic stenosis. A=left atrium; LV=left ventricle; MV=mitral valve; V=aortic valve; AA=aortic annulus (D1); TJ=sinotubular junction (D2). D1=1·7 cm and D2=1·3 m (ratio 76·5%).*

f the systolic murmurs recorded, so that the louder urmurs were associated with the greater sinotubu- r narrowing and the most obviously turbulent flow atterns.

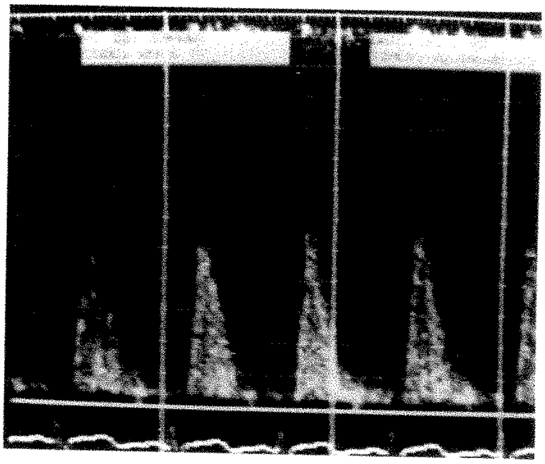


Fig 4 *Pulsed Doppler recording at D3 showing turbulent flow pattern. Peak flow 6 KHz (1·5 m/second).*

Discussion

Accurate non-invasive measurements of children's blood pressures are notoriously difficult to obtain and the group of children and young adults under survey were particularly fidgety. There is a considerable individual variation in children's blood pressures and this may be a factor determining the lower incidence of hypertension in this series compared with the series previously reported where many of the same patients were studied.[6] Hypertension is well described in Williams syndrome, however,[9 10] and it is often thought to be due to renal failure secondary to hypercalcaemic nephrocalcinosis[9] or to unknown causes.[10] Attention has been drawn to the peripheral vascular anomalies coexisting in this syndrome and it has been suggested that hypertension may be related to such anomalies relating to the descending aorta and renal arteries.[4] Our findings support this view as three out of our four patients who had aortic root surgery were hypertensive, and it would seem reasonable to suppose that these patients with severe supravalvar aortic narrowing had other established arterial anomalies. Additionally, we found our patients with abdominal coarctation of the aorta and postoperative thoracic coarctation of the aorta to be hypertensive.

M mode echocardiography of a case of supravalvar aortic stenosis was first reported in 1974.[11] Cross sectional two dimensional scanning, however, can give more precise definition of changes in aortic diameter and the exact location and extent of the stricture. Measurements of aortic root determined in this way compare accurately with angiographic measurements.[12] Using an M mode echocardiogram derived from the sector scan, calculations of cross sectional area at D1 and D2 can be made and they compare accurately with catheter laboratory measurements of pressure differences.[13] Our own findings using cross sectional echocardiography show that supravalvar aortic stenosis is a constant feature of Williams-Beuren syndrome and this may be of useful diagnostic help. Serial aortic root measurements should give adequate information concerning any progression of the supravalvar aortic stenosis in an individual patient. The Doppler recordings were made early in our experience when continuous wave Doppler was not available. The results suggest, however, that Doppler studies should be helpful in assessing severity of stenoses. Preliminary work in progress suggests that continuous wave Doppler may be used to indirectly assess the gradient.

We did not define a case of membranous supravalvar aortic stenosis in our series but confirmed the prevalence of the hourglass type, which is thought to represent thickening of the medial layer of the ascending aorta with narrowing of the corresponding segment of aorta, exaggerated by localised intimal fibrous thickening.[8] Abnormalities of the aortic valve are commonly associated with supravalvar aortic stenosis, the most common variation being adhesion of all or part of the free edge of one or more cusp to the aortic intima.[8] We did not suspect this in any of our patients but we did not happen to include any patients with significant stenosis in the series examined. We did, however, find an 11·6% incidence of bicuspid aortic valves. The common finding of valvar abnormalities in documented supravalvar aortic stenosis and of bicuspid valves in our patients, all of whom had some degree of supravalvar aortic stenosis, might suggest that such patients should be protected from endocarditis with appropriate antibiotics for dental extractions and other surgical procedures.

Reported studies that concern idiopathic hypercalcaemia in Williams-Beuren syndrome and Fanconi type hypercalcaemia are confusing. We feel that the nomenclature of Williams-Beuren syndrome covers our patients, even though some of them had known hypercalcaemia of infancy and some did not. There is also discussion as to the categorisation of supravalvar aortic stenosis that may occur either in sporadic or familial form in individuals of normal intelligence and appearance as well as in individuals recognisable as having Williams-Beuren syndrome.[14] Review of the literature suggests that supravalvar aortic stenosis may also occur in association with facial and other features of Williams-Beuren syndrome, but normal intelligence.[14-16] Again, although Williams-Beuren syndrome usually occurs sporadically, familial cases have been reported.[17-20]

Studies of the histology of supravalvar aortic stenosis have shown that it is common to all types. There is a localised area of disorganised media and of intimal hyperplasia covering narrowing just above the aortic sinuses (hourglass type) and long segment medial induration (hypoplastic type).[8 21] It has been suggested that supravalvar aortic stenosis may be an exaggeration of the infolding immediately above the upper margins of the sinuses of Valsalva, which can often be found in normal infants.[22] Ultrastructural examination of this area in recognised supravalvar aortic stenosis has shown deficiency of the ground substance and foci of excessive collagen deposition in spaces of the elastic lamina, suggesting abnormal prenatal development.[21] Our own finding of supravalvar narrowing, common to all our patients, supports this hypothesis. It has been clearly shown that some newborn rabbits, whose mothers were given large doses of vitamin D, may have supravalvar aortic stenosis[23 24] as well as other arterial narrowing and facial and dental abnormalities.[25] Broadly, it is accepted that there is a disturbance of fetal calcium homoeostasis, but the exact mechanism and its role in the pathogenesis of supravalvar stenosis has not been exactly defined. The finding of a 15% incidence of mitral valve prolapse in our patients was surprising and has not been commented on previously, although two previous cases of mitral valve prolapse have been documented.[16 26]

Defective production or structure of collagen has been shown in type IV Ehlers-Danlos syndrome, Marfan's syndrome, and other hereditary disorders in which mitral valve prolapse commonly occurs.[27 28] A raised collagen III:III+I ratio has been found in skin biopsy specimens of patients with the hypermobility syndrome and floppy mitral valve.[29] An increase in collagen type III in the mitral valve tissue of patients in whom there has been mitral valve prolapse has also been shown. In such valves the collagen fibres of the lamina are disorganised.[30] It has been suggested that biosynthesis of collagen evaluated by in vitro culture of skin fibroblasts with biochemical characterisation of cell products might provide further information concerning the pathogenesis of the cardiac manifestations of Williams-Beuren syndrome.[21]

We do not know how Williams-Beuren syndrome relates to the variable autosomal dominant trait of isolated supravalvar aortic stenosis. It has been suggested that the clinical phenotypes of Williams-Beuren syndrome and supravalvar aortic stenosis represent the ends of a range for an autosomal dominant gene defect of variable expression and penetrance.[31 32] Finally, a terminal deletion of the long arm of chromosome 4 has been reported in Williams-Beuren syndrome[33] and localisation of the calcitonin gene to chromosome 11[34] focuses interest as to whether there is an error in its structure. For the moment, however, the precise causative factors that determine Williams-Beuren syndrome and its cardiac manifestations, particularly supravalvar aortic stenosis as it is seemingly inseparable from this syndrome, remain tantalisingly elusive.

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Antineutrophil cytoplasm antibody in crescentic glomerulonephritis

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SUMMARY Antineutrophil cytoplasm antibody (ANCA) has been reported in the sera of adults with Wegener's granulomatosis and microscopic polyarteritis, but this phenomenon has not so far been described in children. We report three children with crescentic glomerulonephritis in whom ANCA concentrations were raised at presentation. Two cases were idiopathic, and the other later developed features of Wegener's granulomatosis. In all three, plasma exchange and immunosuppression removed ANCA, but in only one case was there clinical improvement. This child later developed classical nasal lesions of Wegener's granulomatosis associated with a decline in renal function and a rise in ANCA. Plasma exchange and immunosuppression again produced a good clinical response and removed ANCA. This suggests that ANCA is either a marker of disease activity, or is involved in the pathogenesis of disease.

Crescentic glomerulonephritis is characterised by intraglomerular extracapillary cellular proliferation and is a relatively rare pathological finding in childhood. It is often associated with the clinical picture of rapidly progressive renal failure. It may be idiopathic or associated with other diseases such as post-streptococcal glomerulonephritis, infective endocarditis, IgA nephropathy, Goodpasture's syndrome, membranoproliferative glomerulonephritis, systemic lupus erythematosus, Henoch-Schönlein purpura, and other systemic vasculitides. The pathogenesis of the histological lesion is incompletely understood.[1]

Microscopic polyarteritis and Wegener's granulomatosis are rare causes of crescentic glomerulonephritis in childhood. Circulating antineutrophil cytoplasm antibody (ANCA) has been described in these disorders in adults,[2-6] but not so far in children. We describe three children with crescentic glomerulonephritis in whom high concentrations of ANCA were detected both by indirect immunofluorescence by overlaying sera on normal neutrophils and by a solid phase radioimmunoassay.

Case reports

Case 1. An 11 year old girl presented in acute renal failure after a one week history of vomiting, abdominal pain, and haematuria. She was oliguric, normotensive, and her plasma creatinine concentration was 603 μmol/l. Despite having no clinical or bacteriological evidence of a recent streptococcal throat infection, she had a raised antistreptolysin O titre of 1200 U/ml (upper limit of normal 400 U/ml), a raised anti-DNAase B titre 600–800 U/ml (upper limit of normal 450 U/ml), and a low C3 concentration of 60% of reference normal serum (normal range 86–118%), suggesting a diagnosis of post-streptococcal glomerulonephritis. She responded to diuretic treatment, but one week after admission her plasma creatinine concentration was still raised at 530 μmol/l, and a renal biopsy was performed. The biopsy specimen contained nine glomeruli, all of which had large cellular crescents and hypercellular tufts (fig 1). Immunofluorescence showed the presence of fibrin in the crescents, but no other immunoreactants were detected. Circulating ANCA was shown in her serum by indirect immunofluorescence on normal neutrophils (fig 2), and confirmed by solid phase radioimmunoassay at a titre of 54% of a positive control (upper limit of normal range 15%).

In view of the severity of the histological changes she was treated with prednisolone 2 mg/kg/day, cyclophosphamide 3 mg/kg/day, and a course of daily 4000 ml plasma exchanges for five days using

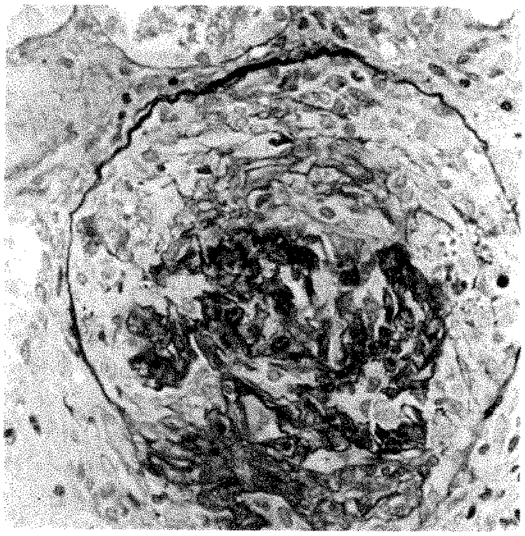

Fig 1 *High power section from the renal biopsy specimen of case 1 showing a glomerulus with a large cellular crescent.*

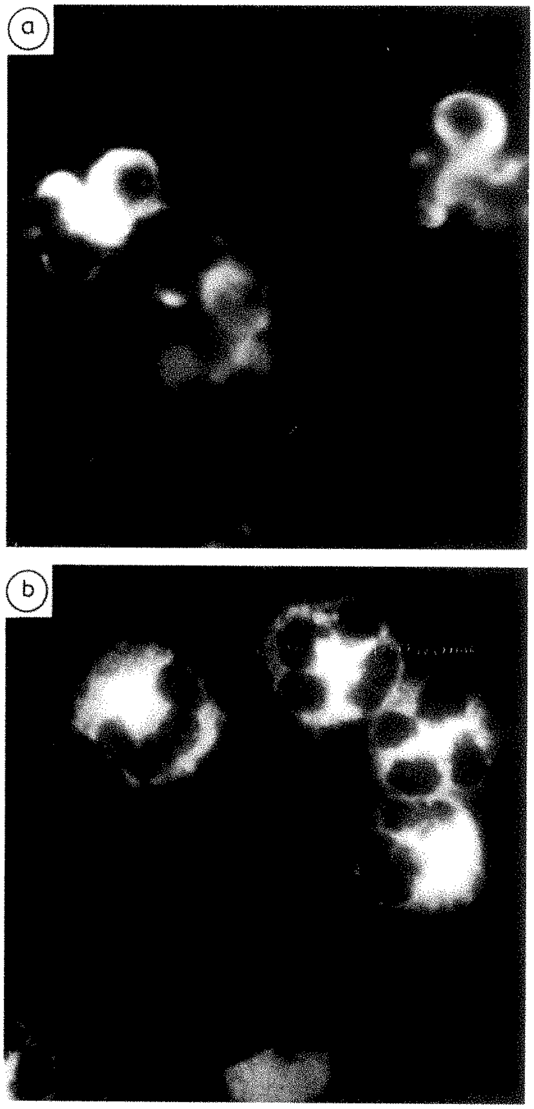

Fig 2 *Detection of ANCA by indirect immunofluorescence. Normal neutrophils are incubated with test serum (diluted 1/8), followed by fluorescein-isothiocyanate-conjugated rabbit antihuman IgG. (a) Serum from case 1; (b) serum from an adult case of Wegener's granulomatosis that has been proved on biopsy. Both show fluorescence of neutrophil cytoplasm.*

purified protein fraction as replacement with fresh frozen plasma for the last 300 ml of each exchange. After this her urine output increased and her plasma creatinine concentration fell to 120 μmol/l. One week later she was discharged home on a reducing dose of immunosuppressives. At this time her ANCA was 11% of positive control (within the normal range), and her glomerular filtration rate was 118 ml/min/1·73 m^2 surface area.

Four months later her glomerular filtration rate had fallen to 70 ml/min/1·73 m^2 surface area, and she developed nasal lesions that were histologically compatible with Wegener's granulomatosis. ANCA had risen to 60% of positive control. Another course of five plasma exchanges combined with cyclophosphamide and steroids again reduced the ANCA concentration to 9% of positive control and her glomerular filtration rate increased to 99 ml/min/1·73 m^2 surface area. One year later she remains well on prednisolone 30 mg on alternate days and azathioprine 100 mg/day with no evidence of recurrence of respiratory tract disease. She has a glomerular filtration rate of 94 ml/min/1·73 m^2 surface area, and has an ANCA concentration measured by solid phase radioimmunoassay of <5% of positive control. Her clinical course and circulating ANCA concentrations are summarised in fig 3.

Case 2. A 12 year old girl presented with a grand mal convulsion after a six week history of vomiting, malaise, and headaches. She was found to be in acute renal failure with anuria, fluid overload, hypertension, and her plasma creatinine concentration was 1560 μmol/l. She was treated by peritoneal dialysis. Initial investigations, which included a normal renal ultrasound, failed to establish the diagnosis. Serum antistreptolysin O titre and anti-DNAase titre were normal, but C3 was 76% of

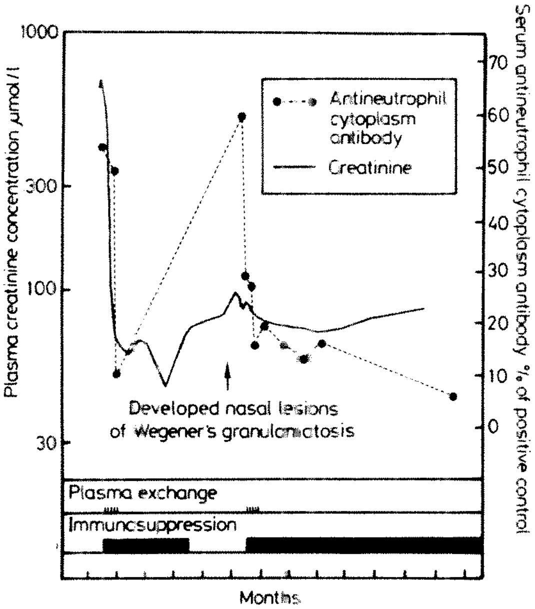

Fig 3 *Clinical course of case 1 showing plasma creatinine concentration and ANCA in relation to treatment*

reference normal serum. She had circulating ANCA shown by indirect immunofluorescence, which when measured by solid phase radioimmunoassay was 41% of positive control. She remained anuric, and a renal biopsy specimen showed all of 60 glomeruli to be severely damaged with predominantly fibrous crescents and sclerosis and hyalinisation of the tufts. Immunofluorescence showed deposits of IgM, Clq, and C3 along the capillary loops.

A course of daily plasma exchanges for five days combined with prednisolone 2 mg/kg/day and cyclophosphamide 3 mg/kg/day reduced the circulating ANCA to 12% of positive control, but she remained anuric. She was entered into a programme for continuous ambulatory peritoneal dialysis but developed peritonitis due to Aspergillus and subsequently an acute meningoencephalopathy of unknown aetiology. This failed to respond to broad spectrum antimicrobial treatment, and despite intensive supportive treatment she died of rapidly progressive neurological disease. A postmortem examination was not performed.

Case 3. An 11 year old girl presented with acute renal failure six weeks after a 10 day illness consisting of sore throat, cough, fever, and haematuria. She was oliguric, fluid overloaded, and hypertensive, and her plasma creatinine concentration was 521 µmol/l. She was treated by peritoneal dialysis. Initial investigations showed an antistreptolysin O titre of 400–600 U/ml, an anti-DNAase B titre of 100–200 U/ml, and a normal C3 concentration of 112% of reference normal serum. She had circulating ANCA detectable by immunofluorescence, which measured by solid phase radioimmunoassay was 32% of positive control. A biopsy specimen showed 36 (95%) of 38 glomeruli to have predominantly fibrous crescents and advanced global sclerosis. Immunofluorescence showed scanty IgM and C3 deposition along capillary loops. Despite a course of daily plasma exchanges for five days combined with prednisolone 2 mg/kg/day and cyclophosphamide 3 mg/kg/day, which removed detectable ANCA, she showed only a transient improvement in renal function. She was entered into a renal replacement programme. ANCA subsequently remained undetectable, and she received a successful renal transplant 13 months after her initial presentation.

Methods

ANCA was detected by two methods:

(1) INDIRECT IMMUNOFLUORESCENCE ON NORMAL NEUTROPHILS

This technique has been described previously.[5] Normal neutrophils from healthy donors are isolated by density gradient centrifugation and alcohol-fixed on glass microscope slides. The slides are incubated for 1 hour at 4°C first with dilutions of test or control sera, and then with fluorescein-isothiocyanate-conjugated rabbit antihuman IgG. The slides are then examined under ultraviolet light, and samples are considered positive if most neutrophils show bright fluorescence in the cytoplasm (fig 2), and negative if no staining is present.

(2) SOLID PHASE RADIOIMMUNOASSAY

This technique has also been described previously.[5] Neutrophil antigen is prepared from normal donor neutrophils by sonication and centrifugation in sodium acetate (0·2 mol/l, pH 4·2), and the supernatant saved. Wells of plastic microtitre plates are coated with the antigen by incubating with the supernatant for 1 hour at 37°C. Dilutions of test or control sera are then incubated in the wells for 30 minutes at 37°C. IgG bound to the wells is detected by a treble-layer technique (mouse monoclonal antihuman IgG, then rabbit antimouse IgG, then ^{125}I-labelled goat antirabbit IgG), and measured by counting in a gamma counter. The results of this binding are expressed as a percentage of the binding seen for a standard positive serum from an adult case of Wegener's granulomatosis that has been proved on biopsy.

Discussion

Crescentic glomerulonephritis is a relatively rare condition in childhood.[1] The severe form can be defined as the presence of crescents in at least 80% of glomeruli and presents as rapidly progressive glomerulonephritis. Only 10 new cases of this severe form have been admitted to the renal unit of the Hospital for Sick Children, London since June 1985 when we started screening these patients for raised ANCA; during this same period we dialysed 171 children with other causes of acute renal failure. In addition to the three cases reported here, three cases were associated with Henoch-Schönlein syndrome, one with anti-glomerular basement membrane nephritis, one with post-streptococcal glomerulonephritis, and two cases were idiopathic. Only the three cases reported here, however, had raised ANCA at presentation. Although ANCA has been shown in the sera of adult patients with Wegener's granulomatosis and microscopic polyarteritis,[2–6] it has not previously been reported in children. In case 1, the diagnosis initially appeared to be post-streptococcal glomerulonephritis despite there being no clinical or microbiological evidence of a throat or skin infection. Four months later, however, she developed clinical symptoms which, supported by histological evidence, established the diagnosis as Wegener's granulomatosis Cases 2 and 3 both appeared to be idiopathic at presentation, but in view of the raised ANCA and the experience from adult cases, might perhaps represent occult microscopic polyarteritis.

The significance of the presence of this antibody is unclear, but a role in the pathogenesis of vasculitis is suggested as its concentration has been shown in adults to decrease as clinical signs of disease activity improve.[6] In the three children described here, plasma exchange and immunosuppression resulted in an appreciable reduction in concentrations of circulating ANCA, but only in case 1 did this coincide with important clinical improvement. She had the shortest history, and in contrast with the others her renal biopsy specimen showed predominantly cellular crescents. When she later relapsed with deterioration of renal function and the development of the nasal lesions of Wegener's granulomatosis, her circulating ANCA concentration had again risen (to 60% of positive control), suggesting that the antibody had either a pathogenic role or was a marker of disease activity.

Circulating ANCA should be sought in children with crescentic glomerulonephritis, and when present may be of diagnostic value, pointing to Wegener's granulomatosis or microscopic polyarteritis. It may also be of value in monitoring the effectiveness of treatment in cases with a short duration of symptoms.

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Urinary infection and malformations of urinary tract in infancy

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SUMMARY One hundred and forty infants with their first urinary tract infections were studied and pronounced differences in age and sex were found. Two thirds of the patients had their first urinary tract infection during the first three months of life, and boys were significantly younger. There was a predominance of boys from 1–3 months old, but of girls thereafter. Obstructive uropathies occurred more often in boys, and during the first two months of life. The incidence of vesicoureteric reflux was similar for both sexes. Malformations recognised after urinary tract infections were compared with urinary tract malformations recognised prenatally. Fetal urinary tracts were evaluated in just over half of all pregnancies during the study period. Obstructive uropathies and multicystic dysplastic kidneys were more often diagnosed prenatally, and most refluxes were diagnosed after the urinary tract infection.

In conclusion age and sex differences are common in urinary tract infection, and even though many urinary tract malformations were diagnosed prenatally this did not influence the high incidence of malformations recognised after urinary tract infection in infancy.

Urinary tract infection is one of the most common bacterial infections in infancy and childhood. Previous studies have reported age and sex related differences in urinary tract infection and urinary tract malformations.[1-5] Though the importance of urinary tract infection during the first year of life is well known, only a few studies concern this particular period.[6-9]

During recent years ultrasonography has improved the diagnosis of urinary tract malformations and enabled us to diagnose them prenatally. We report the data of 140 infants all of whom had what was thought to be their first urinary tract infection and also those of 39 infants with urinary tract malformations diagnosed prenatally during the study period. The first aim of the study was to look for age and sex related differences in urinary tract infection in infancy, and to find out whether these differences are common features or whether they change with time. The second aim was to compare the types of urinary tract malformation detected after urinary tract infection in infancy with the types recognised prenatally, and to find out if prenatal diagnosis can influence the incidence of urinary tract malformations detected after urinary tract infection in infancy.

Patients and methods

During a 48 month period from January 1983 to December 1986, 140 infants all of whom had what was thought to be their first urinary tract infection were admitted to the department of paediatrics. Urine was collected by bladder catheterisation or suprapubic aspiration, and all patients had bacterial counts of $10^5 \times 10^6$/l or more. Most patients had a white cell count of more than 20×10^6/l. Ultrasonography, voiding cystourethrography, and intravenous pyelography were performed in 110 infants. Ultrasonography was the only investigation in 30 patients. Urinary tract malformations were diagnosed prenatally in 39 infants after investigation of the fetal urinary tracts in 17 500 pregnancies. The total number of pregnancies leading to live birth was about 34 000 in our region during the study period. The findings are summarised in the table. Statistical analyses were done by the χ^2 test and Student's *t* test for unpaired data.

Results

The median (range) age of the 140 infants was 3 (4 days to 12 months) at the time of diagnosis.

Thirty eight infants (27%) presented during the first month of life and 80 (57%) during the first 3 months. Only 23 infants (16%) had their first urinary tract infections after they were 6 months old The median (range) age of the 77 boys was 2 (4 days to 10 months) months. They were significantly younger than 63 girls with a median age of 5 (5 days to 12 months) months ($p<0\cdot01$). During the first three months boys had 69% of all urinary tract infections. Later on there was a female predominance, girls having 63% of all urinary tract infections ($p<0\cdot001$). The male:female ratio was 2·2:1 during the first three months and 1:1·7 thereafter; it was 1·2:1 during infancy (figure). Urinary tract malformations were present in 46 infants (42%). There were no significant differences in age or sex among infants with or without malformations. Of the infants with malformations 61% had urinary tract infections before they were 3 months old. The case fatality rate was 44% in this period, but this was not statistically different from the rate of 38% thereafter. Vesicoureteric reflux accounted for 59% of all malformations and obstructive uropathy for 37%. During the first two months 12 of 17 (70%) of all obstructive uropathies were diagnosed. In contrast 66% of all patients with vesicoureteric reflux had their urinary tract infection after they were 2 months old ($p<0\cdot05$). Urinary tract obstructions were significantly more common in boys ($p<0\cdot01$). Vesicoureteric reflux, however, was more common in girls but not significantly so. The incidence of obstructive uropathy was 12% and of vesicoureteric reflux 25%.

Table *Urinary tract malformations detected after first urinary tract infection in infancy and by prenatal diagnosis*

Diagnosis	*Urinary tract infection*	*Prenatal diagnosis*
Obstructive uropathy.		
Ureteropelvic obstruction	8	18
Primary obstructive megaureter	3	7
Duplication with megaureter or ureterocoele	2	1
Posterior urethral valve	4	1
Horseshoe kidney	1	0
Multicystic dysplastic kidney	1	8
Vesicoureteral reflux	27	4
Total	46	39

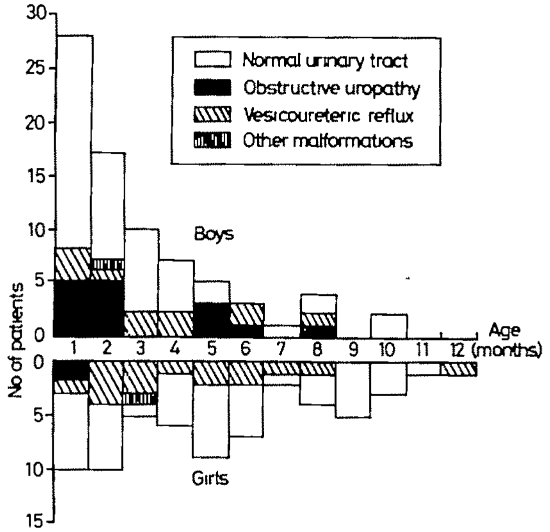

Figure *Age and sex of 140 infants with urinary tract infections*

Forty six per cent of all malformations were diagnosed prenatally. Obstructive lesions and multicystic dysplastic malformations of the kidneys accounted for 90% of all prenatally diagnosed malformations. Of the obstructive malformations 27 of 44 (61%) and eight of nine (89%) of the multicystic dysplastic kidneys were diagnosed prenatally. In contrast, 27 of 31 (87%) of refluxes were diagnosed after what was thought to be the first urinary tract infection.

Discussion

Fifty seven per cent of all urinary tract infections and 61% of all urinary tract malformations were diagnosed during the first 3 months of life; these data show the importance of this early period Later on the incidence of urinary tract infection declined rapidly, but malformations were diagnosed at about the same rate. Malformations encourage infections and therefore contribute to the early development of urinary tract infections. In our patients malformations were not responsible for age and sex related differences. Other factors, therefore, such as the high incidence of haematogenous infections in the first few months of life[10-12] and individual factors such as increased periurethral bacterial colonisation or even the lack of full development of the host defence mechanisms[13] may be responsible. Boys were significantly younger than girls but there is no clear explanation for this. Other studies of urinary tract infection report a female predominance in childhood in contrast to the male predominance in infancy,[1 3 4] but in our series the change in sex predominance took place during the fourth month of life.

Only a few previous studies contain detailed information about malformations diagnosed during infancy, and these report incidences of between

13% and 49%.[1 3 6 8] Our data are within this range, but show a relatively high incidence of obstructive uropathy. Patient selection could be the reason, but the incidence of vesicoureteric reflux indicates that other factors—for example, a high awareness of urinary tract infection, the improved initial evaluation by ultrasonography, and perhaps other local factors—were responsible We can confirm that urinary tract malformations, especially obstructive uropathies, are more common in boys.[1-3 14] Obstructive lesions were diagnosed earlier than vesicoureteric reflux Obstructions are severe congenital malformations and seem to cause more early urinary tract infections than vesicoureteric reflux. In addition, only one part of vesicoureteric reflux is congenital, the other part being secondary to urinary tract infections.

We know of no study that compared urinary tract malformations diagnosed prenatally with malformations diagnosed after urinary tract infections in infancy. Obstructive uropathies ($p<0{\cdot}01$) and multicystic dysplastic kidneys ($p<0{\cdot}05$) were diagnosed more often prenatally. In contrast, most of the cases of vesicoureteric reflux were diagnosed after the first urinary tract infection ($p<0{\cdot}001$). One would expect that the number of malformations especially obstructive lesions and multicystic dysplastic kidneys diagnosed after urinary tract infection in infancy would be reduced by an increase in prenatal diagnosis. Certainly this is true if thorough investigations are performed in all pregnancies. In our region thorough investigation of the fetal urinary tract was performed in just over half of all pregnancies, but though 46% of all urinary tract malformations were diagnosed prenatally, this did not influence the high incidence of malformations diagnosed after urinary tract infection in infancy. Even in our patients who had been investigated prenatally we diagnosed two malformations that were potentially recognisable on prenatal examination namely ureteropelvic obstruction in one infant and a multicystic dysplastic kidney in another. Both were recognised after urinary tract infections in infancy. In general, we found an incidence of 0·2% of prenatal recognisable and primarily not lethal urinary tract malformations.

Our results show that further improvement in prenatal evaluation should be achieved, but even prenatal evaluation in all pregnancies will probably not significantly reduce the number of cases of vesicoureteric reflux detected after urinary tract infection. Thorough investigation by ultrasonography and voiding cystourethrography must be recommended in all infants who have urinary tract infections.

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How parents and families cope with chronic renal failure

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SUMMARY We studied the effects on the family of childhood chronic renal failure by contrasting children with varying degrees of severity of illness with healthy controls. Disruption of family life was most common in families with the more severely ill children (on hospital haemodialysis) and there was a tendency for more mental health problems in the parents in this group. Although more of these parents reported that the child's illness had had an impact on the marriage, marital break up was not related to illness status. There were indications that illness had resulted in an increase of subjective stress but also of support in a number of psychosocial areas for parents, especially those in the more severely affected group. Nevertheless at the time of assessment, fewer mothers in this group were deriving support from their social life and fewer fathers of ill children from their jobs or finances.

It is well recognised that chronic illness in children may result in psychological suffering and social stress for the children themselves and their families, but little systematic research has been carried out in this area. Much still remains unknown about the extent, nature, and implications of family difficulties caused by various childhood conditions.

High rates of parental mental distress have been reported in children with cystic fibrosis and spina bifida,[1 2] but not in a recent study of parents of children with chronic epilepsy.[3] These studies did not use healthy controls and while the variations in the results may reflect different pressures associated with individual conditions, they clearly highlight the need to use comparison groups. The study of the effects of chronic childhood illness on the marriage shows that, although stress on the marriage is often apparent, when control designs are used there is no evidence of raised divorce rates in couples with chronically ill children.[4]

As part of our clinical work in a paediatric nephrology unit we became interested in the psychosocial effects of the illness on families. Previous studies have noted family disruption in children with end stage chronic renal failure, on haemodialysis, or after transplantation.[5–9] These studies, however, were for the most part uncontrolled, they did not differentiate between children at different stages in the condition, nor was the nature of the difficulties always clearly defined.

We decided to study the impact of chronic renal failure on the families with children requiring dialysis when compared with children with less severe forms of chronic renal failure. Because illness may have positive as well as negative effects, in addition to stresses we studied the possible supports mobilised by the illness and considered separately the long term and the current areas of difficulty. The effects of the illness on the psychiatric adjustment of the children themselves were also studied and have been reported elsewhere.[10]

Subjects and methods

All children attending Booth Hall Children's Hospital for a minimum of six months hospital haemodialysis between September 1983 and August 1985 were included in the study. The 22 children (16 boys and six girls with a mean age of 13·8 years) were matched for age and sex with 22 children with chronic renal failure also attending the paediatric renal clinic, but not on dialysis. Children in this latter group all had a creatinine clearance of less than 25 ml/minute/m^2 and were possible future candidates for dialysis or transplantation, or both. Over and above their superior renal function, these children were less severely affected by their illness than children in the hospital haemodialysis group. Their growth was considerably less compromised, and fewer had asymptomatic congestive cardiac failure, were anaemic, or had difficulties running or walking, and there was a tendency for fewer hospital admissions in this group.[10]

A second comparison group of 31 healthy children (21 boys and 10 girls) was studied. Controls for the school age children were selected from four ordinary schools attended by dialysis patients, chosen to represent different socioeconomic areas. Controls for preschool children and school leavers were obtained from the register of a general practice attended by one of the dialysis patients, which covered a socioeconomic area broadly representative of the general population. The first 22 controls were individually matched for age and sex with the dialysis patients, the name of children closest in age to the patients being taken from the class or general practice register. The size of the healthy control group was then increased to allow comparison with the combined sample of ill children, ensuring that the additional group of healthy control subjects was comparable in age with the whole group. All the families in the group on dialysis, 22 out of 23 (95%) of the ill group not having dialysis, and 31 out of 36 (86%) of the healthy families approached for the study agreed to take part.

The age range in the whole group was wide (2 to 18 years, mean of 13 years) including seven preschool children and 14 who had left school: over half the children were of secondary school age. All subjects were living at home with either a parent or guardian. The three study groups were comparable for family variables such as parental age and size of the family. There were no significant differences in socioeconomic level, although there was a tendency towards higher parental unemployment in the group on dialysis, for more parents to be in the manual classes in the ill group not on dialysis, and for more non-manual families to be in the healthy group. Five children came from families with immigrant parents (three in the dialysis and two in the non-dialysis group).

The families interviewed all came from the North West Health Authority region covering a wide geographical area. Interviews were conducted by a social worker with the parents either at home or at the hospital. The assessments of ill children were all made at a relatively stable point in the child's illness and 'crisis' times, such as admissions or important changes in treatment, were deliberately excluded. All parents of children in the study were invited to participate and 65 (89%) mothers and 31 (46%) fathers took part. Nine fathers were interviewed alone: in most cases these were single parents or members of immigrant families where the mother experienced some language problems. One grandmother, with whom the child lived, took part.

A number of methods of assessment were used, either separately for each individual parent or, in some cases, jointly for both.

(1) All parents underwent a structured interview during which they provided detailed information about background family and socioeconomic factors. Details about the children's psychological adjustment were also collected.[10] In addition, parents of ill children provided a description of the illness and its impact on the family.

(2) Current stresses and supports for the parents were assessed with the Social Stress and Supports Interview (SSSI)[11, 12] and current mental distress in parents by the general health questionnaire (GHQ 28).[13] The latter was completed by all but three parents interviewed. For the analysis of data, statistical tests were used as appropriate (χ^2 or Kruskal-Wallis one way analysis of variance).

Results

LONG TERM IMPACT OF ILLNESS ON THE FAMILY

The child's illness was reported to have caused disruption in family life by most parents in the dialysis group (77%) significantly more often than by parents in the non-dialysis group (31%) ($p=0{\cdot}002$). Disturbance was commonly explained in terms of the restrictions imposed by the child's condition or treatment, including dialysis, which made family outings or holidays difficult to organise. Day to day family life was often disrupted with physical care of the ill child taking priority over other activities—such as spending time with the other children, or pursuing hobbies—for example, when there were difficulties in management of a urinary diversion or problems with diet or fluid restrictions. The situation was exacerbated during hospital admissions.

We asked parents about the impact of the child's illness on the marriage and on other specific areas of their lives, about the nature of the impact (whether it had lead to increased stress, to more support, or to both), and about changes in parenting and sibling relationships (figure).

Appreciably more parents in the group on dialysis (65% compared with 27% of parents in the group not on dialysis; $p=0{\cdot}05$) reported that their marriage had been affected. Parents in both groups commonly reported that the illness had had an impact in other psychosocial areas, and this also tended to be more noticeable in the dialysis group. As can be seen from the figure, however, the effects were not necessarily detrimental.

As regards impact on the marriage, as many parents in the group on dialysis reported increased support as increased stress. Changes in financial

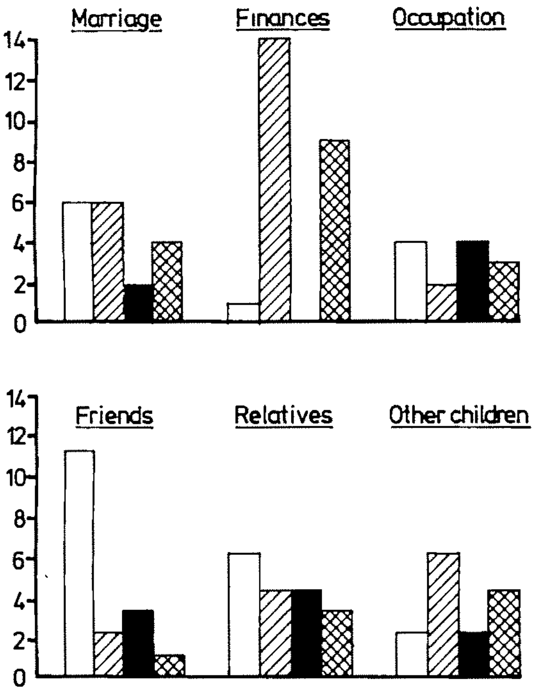

Figure *Impact of illness on aspects of parents' lives. No of parents reporting stressful and supportive changes in the two groups of ill children Parents of group on dialysis (n=22) increased support* □, *increased stress* ▨, *parents of group not on dialysis (n=22) increased support*, ■, *increased stress* ▩.

status were, in all but one family, causing increased stress, usually because of the extra costs incurred through hospital visits and admissions. Impact on the relationship with other children in the family had also been causing stress for both groups There was a trend, however, towards increased support from jobs and in the relationship with relatives and friends.

About 60% of the parents in each group felt that their handling of their children had been affected by the illness and that they had become more protective of the ill child than of their other children. There was a trend for more parents in the group on dialysis than in the group not on dialysis to report increased leniency towards ill children (60% compared with 32%) and to have lower expectations of them (55% compared with 32%) Similarly more parents of children on dialysis perceived changes in siblings' attitudes towards the ill child including worrying, protectiveness, and giving in to the ill child, jealousy by siblings was reported by one third in each group.

MEDICAL CONCERNS AND CONTACTS FOR THE PARENTS

Parents were asked about their concerns connected with the child's illness and about the families' experience of supportive medical contacts. Understandably, prognosis was mentioned most commonly as an area for concern, but just as often parents of patients on dialysis mentioned the child's growth. A few parents voiced concerns about future employment (14% in both groups). Twenty three per cent of the parents of children not on dialysis, but none in the group on dialysis mentioned the children's marriage prospects.

There were clear differences between the groups in the parental perceptions of professional support from medical, social work, and other sources. Parents were asked whether they contacted the hospital if they needed advice or support, other than at routine outpatient visits. More parents of dialysis patients (77% compared with 33%; $p<0.01$) were likely to turn to the hospital saying that they contacted a member of the medical, nursing, or ancillary staff. In addition, all parents in this group said they were in contact with the hospital social worker and saw her as a regular source of support; she was known, however, to only one third of parents of the group not having dialysis—a significant difference ($p<0.001$). Parents were also asked whether they found their general practitioner a support in relation to their child's illness: more parents of the children not having dialysis reported that their general practitioner was supportive (77% compared with 36%; $p<0.02$). Only a few parents in both groups were making use of support from community agencies, such as local social service departments or health visitors Parental satisfaction with the overall support offered from varying sources was higher in the group on dialysis than in the group not on dialysis (77% compared with 32%; $p=0.01$).

CURRENT LEVELS OF PSYCHOSOCIAL STRESS AND SUPPORT IN THE PARENTS

We investigated current psychosocial stresses and supports for the parents at the time of assessment by comparing the two ill groups with controls on the scores from the Social Stress and Supports Questionnaire. Total scores failed to show differences between the three groups in current stress, but there were significant differences in support (table 1) Somewhat surprisingly in view of the long term findings reported before, support was lowest in the group on dialysis (whether the scores of all parents were pooled together or whether the scores of fathers and mothers were analysed separately). When we examined the individual areas of psychosocial support, a different pattern emerged for fathers and mothers. Whereas mothers of dialysis patients reported lower support from their social life with friends than mothers in the other groups (44% compared with 15% and 17%; p=0·05), fathers in both ill groups were experiencing less support than fathers in the healthy group in the areas of finance (54% in the group on dialysis and 33% in the group not on dialysis compared with none of the fathers of healthy children, p=0·01) and occupation (54% and 44% compared with none; p=0·0[illegible]). In line with these findings fewer parents in the ill groups said they had people they could turn to in times of trouble (55% and 58% compared with 84%, p<0·01).

Although parents in the three groups were comparable in the degree of stress and support currently derived from their relationships with other children in the family, significantly more parents of ill children reported schooling difficulties (for example, under achievement, poor concentration, or truanting) among siblings (22% and 20% compared with 1[illegible]%; p<0·005).

MARITAL STATUS AND PARENTAL MENTAL HEALTH

Finally, we considered whether illness in the children and its severity had affected rates of marital breakdown and parental mental health, by comparing the two ill groups with the healthy controls. As will be seen from table 2 no significant differences emerged between the groups. The rates of family break up were comparable, as were those for current mental distress in the parents as measured by scores on the general health questionnaire. Parents interviewed were also asked whether they or their partner had had any recent mental or nerve problems (that is, whether they had consulted their general practitioner during the past two years for their 'nerves' or had taken psychotropic drugs). At a non-significant level there was a clear tendency for mothers of ill children and, to a lesser extent, for fathers of the group on dialysis to report this.

Discussion

Our study confirms previous findings of family disruption in a number of children with chronic renal failure and it shows that this is clearly more noticeable in children with the more severe conditions on hospital haemodialysis There were indications that the illness had had a long term impact on a variety of psychosocial areas including the marriage

Table 1 *Current stress and support for the parents of ill children compared with healthy controls (Results are scores on the Social Stress and Support Questionnaire)*

	Parents of children on dialysis	*Parents of children not on dialysis*	*Parents of healthy controls*	
No of parents interviewed	27	29	41	
Mean (SD) total stress	9·2 ([illegible]·0)	7·2 (4·3)	8 5 (4 5)	NS*
Mean (SD) total support	24·2 ([illegible]·0)	34·2 (3 8)	33 7 (3 1)	χ^2=11 5 p=0 003

*Statistics based on Kruskal-Wallis one way analysis of variance.

Table 2 *Family background and parental mental health for ill children and healthy controls*

	Children on dialysis (n=22)	*Children not on dialysis (n=22)*	*Healthy children (n=31)*
Family background			
No (%) of children from			
Intact family	17 (77)	20 (91)	25 (81)
Single parent	5 (23)	—	4 (13)
Step parent family	—	2 (9)	2 (6)
No of parents with current mental distress/total interviewed (%)*†			
Mothers	6/15 (40)	6/20 (30)	8/29 (27)
Fathers	3/10 (30)	2/9 (22)	2/11 (18)
No of parents with mental/'nerve' problems in last 2 years/total interviewed (%)*			
Mothers	12/20 (60)	11/22 (50)	11/31 (35)
Fathers	3/19 (15)	0/22	1/27 (3)

*Information on parental mental problems refers to all parents with whom children were living at the time of interview All but three parents interviewed (response rate 94/97, 97%) completed the general health questionnaire

†This represents a high score on the general health questionnaire

and parents' mental well being. At the time of assessment, however, there was no significant excess of marital break up or psychiatric distress in the parents and, overall, most families appeared to be coping.

This may be due to the fact that our assessments were carried out at a stable point in the condition, and also that parents reported that over the years the illness had mobilised supports as well as stresses. Our findings on the effects of the illness on the marriage specifically highlight the fact that, although illness often has an impact in this area, it can operate in the direction of increased support. This would explain the lack of a significant increase in marital breakdown in the families of ill children, which is in keeping with Sabbeth and Leventhal's conclusions from their literature review.[4]

The areas in which parents reported difficulties consistently in the past and at the time of assessment were finances and other siblings at home. The findings of increased financial stress for the parents caused by the illness agrees with several previous reports of families with chronically ill children.[5 8] Although some parents in our study were receiving financial help, for example from supplementary benefits or from voluntary hospital funds towards the cost of visiting, many commented that they only learnt about help or benefits to which they were entitled relatively late on in the child's illness.

The illness had also resulted in increased long term stress in the relationship between the parents and other children at home and, in keeping with studies of siblings of children with other chronic conditions,[3 14 15] more parents in our sample reported schooling problems at the time of the assessment. It seems plausible that changes in parenting of the ill child may have caused strain in the parent/sibling relationship and affected sibling development. Our findings highlight this as an area deserving more attention.

Parents had concerns about their children's illness which encompassed both medical prognosis and developmental issues, such as growth. This emphasises the need to take a broad, developmental perspective in the handling of children with chronic illness, and in the supporting of parents. As regards medical support, we did find satisfaction was higher in the group on dialysis where support was offered primarily from the hospital. This raises the question of how best to provide medical and psychosocial support for the families of patients with less severe conditions.

At the time of assessment parents of ill children failed to report more mental health problems or psychosocial stresses than parents of healthy children. Parents of children on dialysis did report fewer supports, however, which can be seen as a sense of decreased satisfaction, security, or well being

Relatively fewer mothers of children on dialysis felt supported in their social life with friends and parents of these children also tended to have fewer people to turn to in times of trouble Ferrari, in a controlled study, similarly found less social support in mothers of children with chronic diabetes[16] This finding might seem surprising in view of the fact that parents of children on dialysis had reported increased long term support. A probable explanation for this apparent discrepancy could lie in the fact that support for parents may be forthcoming on an intermittent basis, particularly at times of acute difficulty or problems in the child's condition. As we were interviewing parents at a relatively stable stage in the illness, this support would not be currently operating. Our findings suggest that mothers with the more severely ill children may be the ones most likely to benefit from regular social or parent groups, where there is an opportunity for contact with other parents in the same predicament.

The areas from which fewer fathers of all ill children derived support were work and finances We noted that some of the fathers commented on finding the demands of work harder to cope with, particularly at times of problems in the child's illness. Other authors have reported work problems in fathers[8] or feelings of resentment when work prevented them from being concerned with treatment and with the child at the hospital.[7] It is worth considering whether a special effort to involve fathers more in various aspects of the ill child's care might result in an increase in their sense of satisfaction with other areas in their lives

It should be noted that our results apply to children on hospital haemodialysis. Previous reports suggest that other procedures, such as home haemodialysis, cause a high level of stress for parents—arising from the degree of responsibility for treatment and the orientation of family life around dialysis.[9 17] In these cases both the need for support and its availability are likely to differ from those identified in our hospital group. Our own results highlight the importance for paediatric and primary care teams to be aware of the vicissitudes of family life in severely ill children, and to direct their support to parents accordingly.

We are grateful to all the families who took part in the study and to the staff at Booth Hall Children's Hospital Dialysis Unit for their help We would like to thank the British Kidney Patients' Association, without whose help this work would not have been possible

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Comparison of temporary and permanent catheters for acute peritoneal dialysis

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SUMMARY The records of 64 children who underwent acute peritoneal dialysis in the Hospital for Sick Children, Toronto, between 1 January 1982 and 31 December 1985 were reviewed. Rigid Trocath catheters were used in 33 patients and silastic Tenckhoff catheters in 34. The groups were comparable for age, weight, primary disease, duration of dialysis, and outcome. There were no significant differences in the incidences of leakage of dialysate, two way obstruction, bleeding, or peritonitis. Among those who had Trocath catheters there were significantly more episodes of outflow obstruction, and significantly more patients required two or more catheter insertions (12 of 33 compared with one of 34 among those who had Tenckhoff catheters). Furthermore, more catheters were removed because of complications (19 of 33 compared with five of 34 respectively). One patient who had a Tenckhoff catheter died of peritonitis directly related to insertion of the catheter. Overall, the Tenckhoff catheter was associated with fewer complications and is recommended for most patients.

Peritoneal dialysis in children was first described by Swan and Gordon in 1949[1] Since then it has been used successfully for the short term treatment of acute renal failure,[2 3] intoxication states,[4] and metabolic abnormalities.[5 6] Until recently nephrologists relied on rigid polyethylene catheters placed percutaneously such as the Trocath (McGaw Laboratories) for acute dialysis. In many centres these have now been replaced by the flexible silicone rubber catheter introduced by Tenckhoff and Schechter in 1968,[7–9] which was originally designed for chronic dialysis. Although the Tenckhoff catheter has been associated with infections and mechanical problems,[10] it has many advantages compared with the Trocath catheter. Its softness allows it to be tunnelled subcutaneously in the anterior abdominal wall, and its Dacron cuffs reduce the incidence of complications such as infection, leakage, and accidental dislodgement. The Tenckhoff catheter, however, is expensive and requires an operation to insert it In children general anaesthesia may be necessary, which delays starting dialysis. Consequently for short term acute treatment the simpler and cheaper Trocath catheter may be a satisfactory alternative. To our knowledge, the two catheters have not been compared for acute peritoneal dialysis. In the present study we reviewed the incidence of complications in acute peritoneal dialysis using either the Trocath or the Tenckhoff catheter.

Patients and methods

The charts of all patients undergoing acute peritoneal dialysis at the Hospital for Sick Children, Toronto, between 1 January 1982 and 31 December 1985 were reviewed. Children with previously recognised chronic renal failure were excluded. Before 1982 all catheters for acute peritoneal dialysis were inserted using the Trocath by the acute stab technique. From 1982 to December 1985 both Trocath and Tenckhoff catheters were used depending on the clinical preference of the responsible physician. In some instances the decision was determined by the patient's clinical condition—for example, surgical placement of a Tenckhoff catheter because of a coagulation disturbance or (rarely) insertion of a Trocath for immediate dialysis because of a life threatening metabolic disturbance such as hyperkalaemia.

Peritoneal dialysis was the treatment of choice and was successfully initiated in all patients The duration of dialysis was recorded from the date of insertion of the catheter to the date dialysis finished. The duration of acute dialysis was limited to 30 days in all cases. Patients dialysed for longer periods were arbitrarily considered to have started chronic dialysis. The techniques used for percutaneous stab followed standard recommendations already reported.[9] Tenckhoff catheters were surgically placed as previously described.[5-6] Heparin or antibiotics were added to the dialysate depending on the individual physician's preference.

All recorded complications were based on the clinical diagnosis of the physicians in charge of the patients. Infections of the exit site or tunnel were diagnosed if redness, swelling pain, and discharge were seen at the site. Peritonitis was diagnosed when a culture showed bacterial growth in association with one or more of the following: cloudy fluid, leucocytosis in the fluid (white cell count of $>50\times10^9/l$ with more than 50% neutrophils), or bacteria seen on a Gram stained smear. A variety of mechanical complications were recorded. Leakage of dialysate was diagnosed when frequent dressing changes were needed, when there was a decrease in the cycle volumes, or resuturing or removal of the catheter were required. Outflow obstructions were diagnosed if there was slow drainage and persistent positive cycle balance, and they required catheter manipulation, irrigation, or removal. Two way obstruction was indicated by slow inflow and outflow and resistance to irrigation. Intraperitoneal bleeding was recorded if bloodstained dialysate was returned after the first three cycles of exchange. Abdominal pain was recorded as a complication if analgesics were required The complication rates were calculated for both groups

Statistical analyses were performed using Student's *t* test and Fisher's exact test where appropriate A p value of <0·05 was considered significant.

Results

From 1 January 1982 to 31 December 1985, 75 children were dialysed for acute illnesses and charts were available for review for 64. Thirty three patients were dialysed using the Trocath, and 34 using the Tenckhoff catheter. Three patients had Trocath catheters inserted first but were given Tenckhoff catheters later; they are included in both groups All Trocath catheters were inserted by stab under local anaesthesia. The location of the catheter was not always recorded In the group who had Tenckhoff catheters, the catheters were inserted surgically, either under general anaesthesia in the operating theatre, n=19 (55%) or under local anaesthesia in the intensive care unit, n=15 (44%). The same surgical technique was used for insertion of all Tenckhoff catheters, and omentectomy was rarely necessary. All children in whom Tenckhoff catheters were inserted under local anaesthesia were sedated, and were already being ventilated as part of their overall management. Heparin was used in 21 of 33 patients in the group with Trocath catheters and 23 of 34 patients with Tenckhoff catheters (p>0·05). Prophylactic antibiotics were added to the dialysate in 14 patients with Trocath catheters and 19 patients with Tenckhoff catheters (p>0·05).

The mean age was 3·41 years (range 2 days to 15 years) for those with Trocath catheters and 3·41 years (range 1 day to 15 years) for those with Tenckhoff catheters. Mean body weight was 15·1 kg (range 1·3–65·9) in those with Trocath catheters and 12·5 kg (range 3·3–32·6) in those with Tenckhoff catheters. There were no significant differences between the groups in age and body weight, and both had the same pattern of primary diseases (table 1).

The mechanical complications associated with peritoneal dialysis are shown in table 2. The most

Table 1 *Primary diseases in patients undergoing acute peritoneal dialysis*

	Group with Trocath catheters (n=33)	*Group with Tenckhoff catheters (n=34)*
Acute tubular necrosis.		
Cardiac operation	6	16
Other causes of shock	9	4
Haemolytic uraemic syndrome	12	10
Poststreptococcal glomerulonephritis	1	1
Interstitial nephritis	1	0
Metabolic abnormalities	4	2
Acute rejection after transplant	0	1

Table 2 *Complications of acute peritoneal dialysis*

	Group with Trocath catheters (n=33) No (%)	*Group with Tenckhoff catheters (n=34) No (%)*
Leakage of dialysate	12 (36)	10 (29)
Outflow obstruction	10 (30)	2 (6)*
2-way obstruction	2 (6)	1 (3)
Dislodgement of catheters	3 (9)	0
Puncture site bleeding	1 (3)	1 (3)
Intraperitoneal bleeding	3 (9)	5 (15)†
Abdominal pain	3 (9)	2 (6)
Fibrin clots in dialysate	3 (9)	3 (9)
Peritonitis	5 (15)‡	5 (15)

*Fisher's exact test, (p<0·01), †one patient with haemorrhagic pancreatitis and one with enterocolitis and bloody ascites have been excluded, ‡one patient in whom peritonitis was present before dialysis has been excluded common problem in both groups was leakage of dialysate, which occurred in 12 patients with Trocath catheters and 10 with Tenckhoff catheters. The leakage was noted during the first 48 hours after catheter insertion in four of the 12 and two of the 10, respectively. Management of those with Trocath catheters comprised decreasing the cycle volume alone in four patients, resuturing in two, and removing the catheter in six. In those with Tenckhoff catheters, one patient required resuturing, one required removal of the catheter and the rest had only the cycle volume reduced. Although the difference in leakage rate between the two groups was not significant, the problem of leakage was more serious in those with Trocath catheters. Outflow obstruction was significantly more common in those with Trocath catheters (10 of 33 patients compared with only two of 34 in the other group, $p<0\cdot01$) and necessitated removal of the catheter in six. In addition, three Trocath catheters accidentally became dislodged. Two catheters slipped out completely, and a third was displaced so that the side holes were outside the peritoneal cavity, causing extravasation of dialysate into the anterior abdominal wall. No such complication occurred in the group with Tenckhoff catheters.

Bloodstained dialysate was seen more often with Tenckhoff catheters than with Trocath catheters (five of 34 compared with three of 33). Two further patients with Tenckhoff catheters bled, from haemorrhagic pancreatitis in one and from enterocolitis with bloody ascites in the other. In the group with Trocath catheters, one patient had severe intraperitoneal bleeding that caused a fall in haemoglobin concentration and required a blood transfusion. All episodes of bleeding subsided spontaneously without either removal of the catheter or laparotomy. Minor complications such as abdominal pain during infusion or draining of dialysate, formation of fibrin clots in the dialysate, or local bleeding from the site of introduction of the catheter, were similar in both groups Interestingly, two patients with Tenckhoff catheters leaked fluid into the thoracic cavity causing a pleural effusion in one, and leakage of fluid from the chest drains and the thoracotomy wound in the other. Only one of these children is included among the 10 patients with Tenckhoff catheters described above as having leakage of dialysate. The reason for leakage of fluid into the chest, which was only seen in patients with Tenckhoff catheters, was not apparent.

The incidence of infections was similar in both groups. Five patients in each group developed peritonitis. The organisms involved were coliforms in four patients, *Pseudomonas* spp. in three, *Candida albicans* in three, *Staphylococcus epidermidis* in three, *Streptococcus pyogenes* in two, and *Staphylococcus aureus* in one. Four patients had peritonitis due to multiple organisms. The time of onset of peritonitis was also similar (nine days in those with Trocath catheters and 10·4 days in those with Tenckhoff catheters, $p>0\cdot05$). Among those with Trocath catheters, two of the five patients had the same organisms cultured from the blood, whereas in the group with Tenckhoff catheters one patient with peritonitis developed septicaemia caused by the same organism. Infections of the exit sites were uncommon, occurring in only one patient in each group.

The patients with Trocath catheters were dialysed for an average of 7·1 days compared with 9·0 days for those with Tenckhoff catheters (table 3), but this difference was not significant. Twelve patients with Trocath catheters required insertion of two or more catheters during the course of dialysis compared to one in the other group. Altogether 19 patients who were given a Trocath catheter initially had to have their catheters removed while they still needed dialysis because the catheters ceased to function and caused complications; this was necessary in only five patients initially dialysed with Tenckhoff catheters. If all mechanical and infective complications were combined, the chance of a complication occurring during dialysis with the Trocath catheter was 45 episodes in 233 patient days or 0·19 episodes per patient day. The corresponding figures for dialysis with the Tenckhoff catheter were 31 episodes in 304 patient days or 0·10 episodes per patient day of dialysis.

Eighteen patients with Trocath catheters and 15

Table 3 *Outcome of patients undergoing acute peritoneal dialysis*

	Group with Trocath catheters (n=33)	*Group with Tenckhoff catheters (n=34)*
Duration of dialysis		
Total patient days	233	304
mean (range)	7·1 (1–15)	9·0 (1–30)
Overall complication rate (Episodes per patient day)	0·19	0·10
Patients for whom catheter removed because of complications	19	5*
Patients requiring two or more catheters	12	1*
Complete recovery	18	15
Chronic renal failure	3	5
Death	12	14

*Fisher's exact test, $p<0\cdot001$.

Table 4 *Causes of death in patients undergoing acute peritoneal dialysis*

	Group with Trocath catheters	*Group with Tenckhoff catheters*
Cardiac failure	4	9
Multiorgan failure	5	2
Cerebral infarction	0	1
Metabolic abnormalities	3	1
Catheter related peritonitis	0	1

with Tenckhoff catheters achieved complete renal recovery and survived. Three and five, respectively, were stabilised by peritoneal dialysis but had persistent chronic renal failure that required continuous ambulatory peritoneal dialysis. Twelve patients with Trocath catheters and 14 with Tenckhoff catheters died despite peritoneal dialysis. With one exception, the cause of death was not related to dialysis (table 4). The only catheter related death was from peritonitis, and this occurred in the group with Tenckhoff catheters

Discussion

The incidence of complications in our patients dialysed with the Trocath catheter was comparable with experience elsewhere. In a series of 184 dialyses in children and adults, Vaamonde *et al* reported leakage of dialysate in 36% of patients, inadequate drainage in 37·5%, intra-abdominal bleeding in 32%, and peritonitis in 6·3%.[11] Valk *et al* reported that 14% of their adult patients having acute peritoneal dialysis had leakage of dialysate, 39% had inadequate drainage, 30% had bleeding, and 3% had peritonitis.[12] Rigden *et al* reported severe bleeding in 4%, and peritonitis in 16%, of the 24 children in their series who underwent acute peritoneal dialysis after cardiopulmonary bypass operations.[13]

We achieved a significant reduction in outflow obstruction with the Tenckhoff catheter. There was also a slight reduction in other mechanical complications although the difference was not significant. Our failure to achieve significance may be due to the small number of patients in the series and the low incidence of complications.

The advantage of the Tenckhoff catheter became more obvious when we considered the number of patients who required a change of catheter or had a catheter removed due to complications. Our study showed that the likelihood of complications was 1·9 times greater with the Trocath than with the Tenckhoff catheter (0·19 versus 0·10, respectively). If we accept the increased number of mechanical problems with the Trocath catheter, however, and are prepared to replace it when indicated, patients can be dialysed effectively with either catheter, as shown by the similar outcome in our two groups. Although the Tenckhoff catheter led to fewer complications, it did not eliminate them, especially the life threatening problems such as peritonitis Ironically the only catheter related death in our series occurred in a patient dialysed with the Tenckhoff catheter.

We attempted to minimise errors due to selection bias by including in our study all available patients who met our preset criteria and by explicitly defining complications and the time period of the study to maintain consistency throughout. Nevertheless some complications may have been missed because not all charts were available for review and some complications may not have been documented. This may have led to inaccuracies in this study. Although the type of catheter inserted in some cases may have been influenced by the patient's clinical condition, such a decision would usually have placed the higher risk patients in the group receiving the Tenckhoff catheter in which there were fewer complications.

The present study supports our belief that the Tenckhoff catheter is better than the traditional Trocath catheter even for short term peritoneal dialysis Our results are based on retrospective uncontrolled data, however, and should be interpreted with appropriate caution.

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Reflex anal dilatation associated with severe chronic constipation in children

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SUMMARY Data were collected from children with severe chronic constipation, and the appearance of the anus at presentation was noted. A visibly relaxed sphincter (indicating a degree of reflex anal dilatation) was seen in 20 children out of the 129 in whom this sign was sought. The only differentiating characteristic in this group of children was the greater degree of faecal loading judged on palpation of the abdomen. This evidence supports the hypothesis that constipation of such severity that it was referred to a specialised clinic can produce signs that may lead to an erroneous diagnosis of sexual abuse by anal penetration.

There have been a number of reports urging caution about the diagnosis of sexual abuse in children based on physical evidence alone.[1] [2] These followed the paper by Hobbs and Wynne[3] that described the importance of the anal appearance in children who had been abused. The controversies in both the medical and popular press, and the evidence presented to the Cleveland child abuse inquiry, led me to review details of a long term follow up study of children who had presented with chronic constipation. The standardised history and examination of these children included a record of whether the anal sphincter was visibly relaxed on inspection at the child's first visit.

When the rectum is distended naturally by the arrival of faeces, or artificially by the inflation of a balloon, the internal anal sphincter is inhibited. This anorectal reflex is mediated by the myenteric nerve plexus and modified by the spinal nerves. The reflex is absent from the Hirschsprung's aganglionic segment[4] but exaggerated in the neurogenic rectum. The anorectal reflex was first described in dogs in 1877 by Gowers[5] and in 1935 Denny-Brown and Robertson described it in man.[6] In a non-constipated control group (n=24) the reflex was seen clearly on anal manometry in all but one patient.[7] I had therefore expected to see reflex anal dilatation in all those children who had pronounced faecal loading palpable on abdominal examination, and not in that small proportion of children who had extremely short segment Hirschsprung's disease. I found it impractical, however, to look for this sign routinely as it was often difficult to inspect closely if there was a lot of soiling, and often children were reluctant to be examined in such a way on the first visit to the clinic. Nevertheless I report the findings in 129 children who presented to this tertiary referral centre with chronic constipation between 1979 and 1983 in whom the state of relaxation of the anal sphincter on inspection was recorded.

Details of the child's history with special reference to symptoms of constipation, soiling, anal discomfort, blood passed from the rectum, previous treatment, family background, and social and psychiatric factors were collected on standard questionnaires and the data stored on computer. Details of some aspects of the examination were also recorded including the degree of faecal loading assessed from palpation of the abdomen, and whether the anal sphincter appeared relaxed.

Patients

Data were available for 129 children, of whom 75 (58%) were boys. Their mean age at examination was 5·4 years (range 1·3–15·5).

Results

Of the 129 children 20 (15%) had visibly relaxed sphincters; 14 (70%) of the 20 were boys compared with 61 of 109 (56%) in the non-relaxed group. The degree of faecal loading felt on abdominal examination was graded from 0 (no faeces felt) to 6 (faeces palpable to the level of the ribs). Faeces palpable to level of umbilicus scored 3. The group with relaxed sphincters had more faecal loading than the non-relaxed group (table 1), which confirms the associa-

Table 1 *Differences in faecal loading grades*

Faecal loading grade	*Relaxed group No (%)*	*Group not relaxed No (%)*
0	0	59 (54)
1	5 (25)	12 (11)
2	4 (20)	18 (16)
3	8 (40)	15 (14)
4	2 (10)	1 (1)
5	1 (5)	3 (3)
6	0	1 (1)
Total	20 (100)	109 (100)

tion between faecal loading palpable on abdominal examination and the visibly relaxed sphincter.

There was no difference in the age at presentation between the groups, the mean (SD) age of the group with relaxed sphincters was 5·6 years (2·45) and for the non-relaxed group 5·33 years (3·07). Table 2 shows the usual bimodal distribution of the age of onset of chronic constipation with no obvious skewing of the data in the group with relaxed sphincters.

I routinely recorded my impression of the child at the end of the first or second consultation; though this is only a rough guide to the behaviour in the consulting room, the assessment was made without bias in relation to sexual abuse as it was done before the current emphasis on the reflex anal dilatation sign was published. Table 3 shows that there were no differences in behaviour between the two groups

A subjective grading was also made routinely of the overall features in both history and examination that suggested that psychological factors may have been playing a part in the cause or persistence of the bowel symptoms. This impression of the child and family has previously been shown to correlate with a more detailed accumulated score of psychiatric factors calculated from a number of behavioural, familial, and environmental variables collected in the standardised questionnaire[7] The group with relaxed sphincters had less psychiatric disturbances than the non-relaxed group.

I also correlated the appearance of the sphincter with the previous treatments in case the appearance of the anus depended on whether anal penetration by therapeutic agents was the cause of the relaxed sphincter. Table 4 shows little difference between the groups in the treatments which had been given before referral to the clinic. The group with relaxed sphincters had received slightly more invasive treatment as would be expected from the increased severity of their constipation as judged by the degree of faecal loading.

The hospital case notes were traced for 18 of the 20 children who had relaxed sphincters; table 5 summarises the major features. In only one case was there a number of features that might have suggested sexual abuse; case 19 had extremely mild constipation, failed to attend for follow up examination, and his parents did not reply to a letter. He was admitted to his local hospital having taken an overdose of aspirin at the age of 5 years. His mother was contacted by telephone and said that he had

Table 2 *Age of onset of constipation and anal appearance*

Age of onset	*Relaxed group No (%)*	*Group not relaxed No (%)*
<1 month	4 (20)	25 (23)
1–5 months	4 (20)	18 (16)
6–12 months	4 (20)	9 (8)
1–2 years	3 (15)	20 (18)
2–3 years	4 (20)	24 (22)
4–6 years	0	7 (6)
6–8 years	1 (5)	1 (1)
8–10 years	0	1 (1)
10–15 years	0	4 (4)
Total	20 (100)	109 (100)

Table 3 *Observer's description of child's behaviour*

Description	*Relaxed group No (%)*	*Group not relaxed No (%)*
Normal	15 (75)	77 (71)
Shy	2 (10)	9 (8)
Aggressive	0	1 (1)
Retarded	1 (5)	4 (4)
Immature	0	7 (6)
Anxious	1 (5)	8 (7)
Depressed	1 (5)	2 (2)
Other	0	1 (1)
Total	20 (100)	109

Table 4 *Invasive treatment and anal appearance*

Treatment	*Relaxed group No (%)*	*Group not relaxed No (%)*
Suppositories	15 (75)	71 (65)
Enemas	8 (40)	36 (33)
Anal dilatation under general anaesthesia	2 (10)	8 (7)
Total	20 (100)	109 (100)

Eight (40%) of the relaxed group and 30 (28%) of the not relaxed group had both enemas and suppositories, two (10%) of the relaxed group and five (5%) of the not relaxed group had had all three types of treatment

Table 5 *Features of children with visibly dilated anuses when they presented with chronic constipation*

Case No	*Date at presentation*	*Age (years)*	*Degree of faecal loading*	*Diagnosis*	*Surgical treatment*	*Psychological features*	*Follow up*
1	January 1980	6·7	1	Megarectum	Anal dilatations (2)	None	Still taking laxatives after 63 months
2	December 1979	5·5	3	Megarectum	Anal dilatation (1)	Caravan home	Rapid improvement especially after rehousing
3	May 1981	3·0	2	Normal colon, constipation from birth	None	Slight speech delay only	Not taking laxatives after 4 months
4	December 1980	1·3	3	Anteriorly placed anus	None	None	Not taking laxatives after 4 months
5	November 1979	5·5	3	Megarectum	Anal dilatation (1)	None	Not taking laxatives after 43 months
6	December 1980	3·3	4	Mild megarectum	Anal dilatation (1)	Problems with pot-training	Not taking laxatives after 10 months
7	December 1979	6·5	3	Megarectum	Anal dilatation and internal sphincterotomy	None	Not taking laxatives after 49 months
8	February 1980	5·0	1	Anal fissure	None	Pain during pot-training	Not taking laxatives after 4 months
9	February 1981	12·0	3	Anal stenosis	Anoplasty	None	Not taking laxatives after 24 months
10	November 1979	6·0	5	Megarectum	Anal dilatation (1)	Helped by education welfare officer	Lost to follow up
11	January 1982	3·0	1	Megarectum	Anal dilatation (1)	None	Not taking laxatives after 15 months
12	April 1981	1·8	4	Megarectum	Anal dilatation (1)	None	Not taking laxatives after 61 months
13	March 1979	3·5	3	Megarectum, high anal stricture (5 cm)	Anal dilatation and internal anal sphincterotomy	Receiving psychotherapy	Not taking laxatives after 75 months
14	December 1979	3·9	1	Mild megarectum	Anal dilatation (1)	Speech delay; fear of lavatory, receiving psychotherapy	Not taking laxatives after 13 months
15	April 1982	8·0	3	Huge megarectum	Anal dilatations (4)	Stutter; receiving psychotherapy	Still taking laxatives
16	March 1982	6·0	3	Megarectum, bladder diverticulae	Anal dilatation (1)	Highly strung, sensitive	Took senna occasionally after 26 months
17	December 1979	6·5	2	Megarectum, large anal skin tag	None	Pain during pot-training	Not taking laxatives after 10 months
18	October 1983	5·0	1	Mild rectal loading	None	Took overdose of aspirin aged 5 years	Did not attend for follow up or respond to letter
19			3	Hospital records unavailable			
20			2		Anal dilatation (1)	Not known	Not taking laxatives after 9 months

stopped soiling, was still reluctant to pass stools and tended to accumulate them but did not require regular laxatives There had been no overt psychiatric problem and his slight slowness at school was caused by difficulty in hearing that was being treated.

Discussion

These data support the hypothesis that the anal appearances that are said to be characteristic of anal penetration in children who have been sexually abused may be mimicked by chronic constipation. The other features in the history, examination, and progress of the children who had first been recorded as having visibly relaxed sphincters 10 years ago suggested that the difference between them and the children in whom this sign was not seen was the degree of faecal loading. There seemed to be no more psychiatric disturbances among those with relaxed sphincters, and nothing in their subsequent history to support the belief that they had been abused. In only one of the 20 children was there a suspicious later history (case 18, table 5), but there have been no further symptoms during the subsequent four years and no extra help has been sought by his mother despite a recent offer.

It is possible that we may have missed other evidence that some of the children we had assumed to be only constipated had in fact been sexually abused I have followed up a number of these children personally; their signs always came and went depending on the state of their bowels and so I am confident that I am right in recommending care in the interpretation of this sign. Family or individual psychotherapy has in some cases brought to light possible evidence of sexual abuse of children; occasionally children have produced symbols in their drawings that are highly suggestive of a previous violation or assault. Sadly, this can sometimes be seen as having arisen as a result of coercive or invasive treatment such as enemas or suppositories given without adequate sedation. It is impossible for children to separate these experiences clearly from deliberate sexual abuse; this is an important warning to those managing children with constipation as well as being another factor that may lead to confusion unless interviews are carried out with extreme care and with knowledge of what treatment the child has already undergone.

The evidence here is obviously confined to children with severe constipation. There is also debate on whether reflex anal dilatation occurs in normal, healthy children who have not been abused. Too little is known about the normal appearance of the anus in healthy children at different ages. A control study of a large cohort of volunteers is greatly needed but there are obvious ethical problems in recommending recurrent inspection of the anuses of otherwise healthy children.

The normal anal sphincter relaxes in response to a rectal contraction (the anorectal reflex). This is often seen in the resting record during anorectal manometry As the pressure rises in the rectum the pressure in the anus falls. It may be that emotions that increase colonic and rectal activity could increase the frequency of spontaneous rectal contractions and the associated reflex anal dilatation. Whether a clinical examination could produce sufficient stress to produce this effect in the absence of previous abuse or constipation is open to question; it is also possible that anxiety or fear could exaggerate this normal reflex.

I am sure that many children have been sexually abused and that this has not been diagnosed. Many adults have reported how such experiences have spoiled their lives. This has understandably led to doctors becoming more vigilant in order to protect children and, if they have already been abused, to prevent further harm. Many parents of abused children have been unaware that the other parent was abusing the child, and I am equally sure some have even tried to hide it from themselves but have had a compulsion to continue. Children may be too young or too frightened to ask for help even from a relation. Doctors are expected to do all they can to safeguard children, and there are tragic results when they (or social workers) fail to prevent abuse.

Every action taken to protect a child is the result of a difficult decision, and that is why it requires a careful legal procedure. To compare this protection with a safety net, problems may arise if the mesh of the net is too narrow or too wide. If we have a system in which it is so tight that not a single case of abuse is missed, then it is almost certain that innocent people will be wrongly accused. If the mesh is too loose, some cases of abuse will be missed, but it is unlikely that innocent families will be disrupted It is for society to choose in which direction we should lean, and thereby potentially err. I feel that because of the unreliability of the anal signs described the present system is dangerously close to erring badly in the direction of disrupting innocent families.

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Short reports

Vomiting and gastro-oesophageal reflux

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SUMMARY During radionuclide scans in 82 infants and children gastro-oesophageal reflux extending to the upper oesophageal/laryngeal level was detected in 636 one minute frames. Only 61 (9·6%) of these frames were associated with vomiting, defined as the appearance of milk at the mouth. Thus the absence of vomiting does not preclude appreciable gastro-oesophageal reflux.

Vomiting (or the presence of regurgitated feeds at the mouth) is recognised as the clinical hallmark of gastro-oesophageal reflux in infants. The clinician is often faced, however, with the situation where symptoms such as recurring chest infections, haematemesis, or irritability—particularly in a handicapped child—might be attributable to gastro-oesophageal reflux without clinically prominent vomiting.

We studied 82 infants using prolonged radionuclide scanning to detect gastro-oesophageal reflux and noted its frequent occurrence without clinically observed vomiting. This paper reports the relation of gastro-oesophageal reflux with vomiting in these studies.

Subjects and methods

Eighty two infants and children were studied by radionuclide scan.[1] They comprised 22 children who had had a 'near miss' for sudden infant death syndrome (SIDS); 12 siblings of previous SIDS victims; a miscellaneous group presenting with symptoms that were apparently not life threatening· choking episodes (n=29), recurrent wheeziness perhaps related to tracheobronchial aspiration (n=7), recurrent vomiting (n=8); and four children with mental retardation. The mean age was 0·36 years (0·03–1·79 years)

Gastro-oesophageal reflux was detected by radionuclide scans performed with a Siemens ZLC gamma camera and computer with a low energy all purpose collimator (NEMA sensitivity 6·0 counts/second/μCi). All the infants were fasted for at least four hours before a scan and were then fed freshly prepared ^{99m}Tc sulphur colloid mixed in a small amount of the infant's normal feed (either formula or expressed breast milk) The mean (SD) isotope dose administered to each infant was 7·76 (0·66) MBq giving an estimated reflux detection threshold in the region of 2–5 ml/second allowing adequate visualisation of episodes of reflux in the infants studied.

After the isotope/milk mixture the infant completed the remainder of his or her normal feed, was winded and then settled on the gamma camera face. Care was taken to remove any of the infant's clothing or coverings contaminated by spillage or vomiting of radioactive material during the study and if activity persisted in the nasopharynx after gastro-oesophageal reflux a small amount of non-radioactive feed was given to clear the pharynx.

The gamma camera was set to accumulate counts for 60 seconds every 60 seconds (that is, one 60 second frame was collected every 60 seconds) and the results were displayed on a monitor and stored in the gamma camera computer before subsequent transfer onto floppy disc at the end of each study to provide a long term record. The scan studies lasted on average a mean (SD) of 110 (17) minutes. Gastro-oesophageal reflux on milk scan was assessed visually during each study by one observer (JYP) who noted 'moderate' reflux (affecting only the lower oesophagus) or 'severe' reflux (extending to the upper oesophagus or larynx) during the course of the scans. A minute to minute recording of time was made simultaneously. The occurrence and time of milk appearing at the mouth (vomits) was also noted

Results

Gastro-oesophageal reflux exceeding a threshold of 2–5 ml/second was detected in 883 frames each lasting 60 seconds. In 636 frames the reflux extended

Table *Gastro-oesophageal reflux and vomiting in 'milk' scans (n=82)*

	Gastro-oesophageal reflux detection on scans*		
	Severe	*Moderate*	*Total*
Frames	636†	247	883
Episodes	272	138	410

*Severe = reflux to upper oesophageal/laryngeal level; moderate = reflux into lower oesophagus only.
†Sixty one frames corresponded to 61 clinically evident vomits.

to the upper oesophageal level. The 636 frames represented 272 episodes of gastro-oesophageal reflux lasting one or more minutes.

Clinically obvious vomiting occurred on 109 occasions, at least once during the course of scanning in 43 infants. These 43 infants comprised 15 who had had a 'near miss' for SIDS, five siblings of SIDS victims, 10 who had choking episodes, four who had suspected aspiration, seven with recurrent vomiting, and two with mental retardation.

The table gives the results for gastro-oesophageal reflux and vomiting during the course of the scans. Although all vomits were accompanied by the appearance of milk at the infant's mouth, only 61 out of 109 (56%) were associated with discernible change in oesophageal activity on the gamma camera image. The remaining 48 (44%) vomits were associated with amounts of reflux that were too small to exceed the critical volume/duration threshold previously defined in vitro.[2] Conversely, of 82 scans with gastro-oesophageal reflux to the upper oesophageal level in 636 frames vomiting was only noted on 61 frames (9·6%). When data were reanalysed retrospectively the corresponding figure was 9·8%. Vomiting is a specific but not a sensitive marker of gastro-oesophageal reflux.

Discussion

These results show that gastro-oesophageal reflux, often to upper oesophageal level, often occurs without associated vomiting. When vomiting is present it is likely to represent a tip of an 'iceberg' of gastro-oesophageal reflux. Sutphen and Dillard have also noted that a history of vomiting in infants, alone or in combination with other symptoms, is not a satisfactory predictor of the amount of reflux detected in the lower oesophagus using prolonged lower oesophageal pH monitoring.[3]

These observations are of relevance to situations where gastrointestinal, pulmonary, or neurological symptoms might be related to gastro-oesophageal reflux but where vomiting is not a prominent feature. The absence of vomiting does not preclude gastro-oesophageal reflux as the cause of the symptoms.

In situations where symptoms may be attributed to gastro-oesophageal reflux, but vomiting is uncommon or absent, sensitive techniques must be employed if the diagnosis is not to be overlooked. The method commonly used for detecting gastro-oesophageal reflux is the barium swallow with delayed imaging[4] which may detect up to 85% of cases.[5] A major limitation of radiological techniques is the necessary restriction of exposure time to minimise the radiation dose thereby increasing the likelihood of missing intermittent episodes of gastro-oesophageal reflux. The viscosity of the contrast medium can also affect the occurrence of gastro-oesophageal reflux, and for these reasons barium studies may fail to detect it and lead to misleading reassurance. In such situations, testing over more prolonged periods of time by techniques such as radionuclide scans or lower oesophageal pH monitoring may be needed if appreciable gastro-oesophageal reflux is not to be missed. Unfortunately data on the amount of reflux that would be expected on radionuclide scans on normal infants is not available. Seibert *et al* compared one hour radionuclide scans and 24 hour pH studies and found that only one episode of reflux was necessary on a one hour radionuclide study for a subsequent 24 hour lower oesophageal pH study to be positive.[6] By this criterion it seems likely that many of the infants we studied had appreciable gastro-oesophageal reflux.

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Body segments and growth hormone

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SUMMARY The effects of human growth hormone treatment for five years on sitting height and subischial leg length of 35 prepubertal children with isolated growth hormone deficiency were investigated. Body segments reacted equally to treatment with human growth hormone; this is important when comparing the effect of growth hormone on the growth of children with skeletal dysplasias or after spinal irradiation.

There are only a few reports about sitting height and subischial leg length in children who are growth hormone deficient and being treated with human growth hormone, and none of these studies has been for more than two years.[1 2] We describe the effects of human growth hormone treatment for five years on height, sitting height, and subischial leg length in 35 prepubertal children with isolated growth hormone deficiency

Patients and methods

Thirty five children (25 boys, 10 girls) who were prepubertal throughout the treatment period were studied. Mean chronological age of the patients at the start of treatment was 7·5 years (range 2·2–12·7 years) and bone age 5·6 years (range 1·0–9·7 years).

Patients were measured at intervals of three months for at least one year before treatment and during the first two years of human growth hormone treatment and subsequently every six months. Subischial leg length represents standing height minus sitting height. To allow comparison between different ages and between sexes, all measurements were expressed as a standard deviation score (SDS) for both chronological age and bone age.[1 3] Bone age was assessed annually using the TW2 method.[4]

Growth hormone deficiency was diagnosed by a growth velocity less than the 25th centile for age for two years or more and a growth hormone response of less than 15 mU/l to insulin induced hypoglycaemia. This test was combined with pituitary stimulation using intravenous thyrotrophin releasing hormone (200 µg) and gonadotrophin releasing hormone (100 µg) All patients fulfilled the Health Services Human Growth Hormone Committee requirements for treatment with human growth hormone. Human growth hormone was administered three times a week using doses of 12 or 15 units per week.

Analysis of variance of repeated measurements was used to assess differences between the means of height, sitting height, and subischial leg length in each treatment year compared with the pretreatment year. The Newman-Keuls test was applied to assess the significance of the differences between means

Results

Height SDS, sitting height SDS, and subischial leg length SDS for chronological age and bone age in all treatment years are shown in the figure. SDS for chronological age for all three parameters increased significantly throughout the treatment years, but

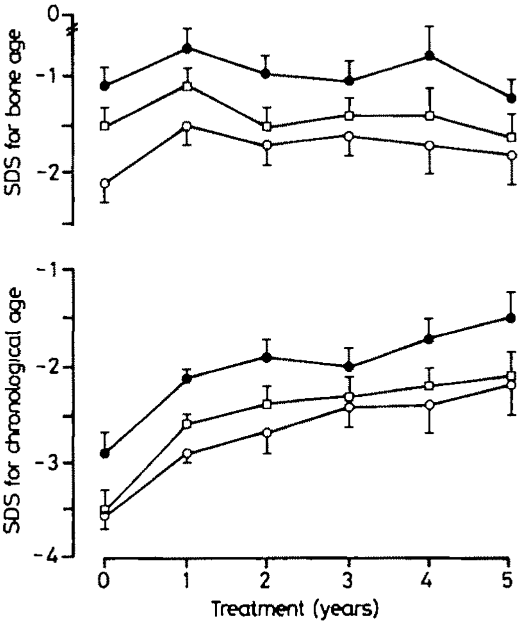

Figure *Changes in height (□), sitting height (○), and subischial leg length (●) SDS for chronological age and bone age during growth hormone treatment. Data shown as mean (SEM).*

SDS for bone age did not change. The difference between mean sitting height SDS and mean subischial leg length SDS remained unchanged over the five year study period.

Discussion

The availability of large quantities of biosynthetic growth hormone have stimulated many investigators to use this agent in short children who are or are not growth hormone deficient such as those with dysmorphic syndromes skeletal dysplasias, and normal short stature. The effect of growth hormone treatment on body segments therefore becomes an important consideration. We have compared the growth of upper and lower segments in children with isolated growth hormone deficiency. Although caution needs to be exercised in the interpretation of sitting height standards (SM Herber, RDG Milner. Have sitting height standards changed? Abstract G87; 58th Annual Meeting of the British Paediatric Association, York, 1986.), our results confirm that sitting height and subischial leg length react equally to human growth hormone treatment in prepubertal children over many years of treatment. Growth hormone treatment in these children prevented further loss in stature which would ensue if treatment had not been initiated. Growth hormone treatment, however, did not improve the height prognosis at the commencement of treatment, as judged by little change in height SDS for bone age. Instead it ensured that the child's remaining growth was 'normalised'.

These findings have important implications. We would predict that the response of children who have skeletal dysplasia to growth hormone will not be as much as might be expected because of a lack of either the spinal or lower limb component or both to the growth response to growth hormone treatment. Similar findings have been observed in children who have received craniospinal irradiation and been treated with growth hormone.[5] Changes in standing height in such individuals should not be used to define response but rather the change in body segments should be calculated.

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Fatty liver and medium chain triglyceride (MCT) diet

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SUMMARY A 12 year old boy with intractable epilepsy developed fatty infiltration of the liver after three years' treatment on the medium chain triglyceride (MCT) diet. This was not associated with any hepatic dysfunction and resolved after discontinuing the diet. Three of four other patients on the same diet had evidence of hepatic steatosis.

Ketogenic diets for the treatment of intractable epilepsy have been used for over 60 years. In 1986 Sills *et al*, working at Leeds General Infirmary, reported the beneficial effect of the medium chain triglyceride (MCT) diet on the treatment of epilepsy in childhood.[1] Adverse side effects have included mild abdominal pain and diarrhoea, and one patient suffered transient blindness when vitamin supplementation was omitted. More recently we have been aware of the problem of fatty infiltration of the liver.

Case report

The patient, a boy, had been noted at birth to have

Table *Clinical details of the five epileptic patients on the MCT diet who had abdominal ultrasound scans*

Case No	*Age (years)*	*Diagnosis of epilepsy*	*Drugs*	*Duration of diet (years)*	*Results of investigations*		
					Ultrasound scan	*Liver function tests*	*Triglycerides and cholesterol*
1	12	Astatic myoclonic	Clobazam	3	Abnormal†	Normal	Normal
2	8	Astatic myoclonic	Sodium valproate, clobazam	2	Abnormal†	‡	‡
3	4	Astatic myoclonic	None	3	Abnormal†	Normal	‡
4	8	Astatic myoclonic	Carbamazepine	2	Abnormal†	Normal	Normal
5	20	Grand mal	Primidone	3*	Normal	‡	‡

*This patient had very poor dietary compliance

†Abnormal ultrasound scan with increased echogenicity of the liver

‡Test not performed

prune belly syndrome and had required surgery at the age of 2 months to reimplant his left ureter. At the age of 6 he had presented with tonic clonic seizures that were initially controlled with sodium valproate. At the age of 7½, however, he had developed astatic myoclonic epilepsy that was drug resistant. At 9 years of age he was started on the MCT diet with considerable improvement in his seizure control.

At 12 years of age an abdominal ultrasound examination, which was performed after a urinary tract infection, showed evidence of bilateral hydronephrosis and hydroureters that was associated with a thick walled distended bladder indicating bladder outflow tract obstruction. At the same examination the liver was noted to show mild enlargement and an abnormally fine and highly reflective echo pattern. This incidental finding was strongly suggestive of fatty infiltration. Further investigation of hepatic function showed normal liver function tests and normal concentrations of serum triglycerides and cholesterol. The MCT diet was discontinued and four weeks later a repeat ultrasound scan showed diminution of the echogenicity of the liver though the scan was still abnormal. A laparotomy was performed for surgery on the renal tract and a liver biopsy specimen taken at this time showed diffuse fatty infiltration of the liver. Repeat abdominal ultrasound scans one month and three months after surgery showed complete resolution of the previous hepatic abnormalities.

Abdominal ultrasounds were undertaken in four other epileptic patients who were on the MCT diet. Three of these patients showed a diffusely bright liver on abdominal ultrasound scans suggestive of fatty infiltration of the liver. The fifth patient had a normal scan but it was notable that she had poor dietary compliance (table).

Discussion

For many children the MCT diet has had a profound effect on the control of their epilepsy. Side effects previously reported have been minimal—namely abdominal pain and diarrhoea—though Livingston reported that children on the diet failed to grow.[2] We have been unable to find any other reports of the effects of the ketogenetic MCT diet on hepatic function in children.

The mechanism of fatty infiltration of the liver is unclear. Potentially there are three mechanisms whereby fatty infiltration may occur. Firstly from increased dietary intake, secondly from the direct metabolic changes within the liver, and thirdly from breakdown of the fatty acid pool of adipose tissue. In other disease processes where the MCT diet has been used hepatic steatosis has not been described. The quantity of MCT used in these diets, however, is not sufficient to produce ketosis. Medium chain triglycerides are absorbed directly from the gastrointestinal tract in the form of medium chain fatty acids. These are carried directly to the liver by the portal vein where they are converted to carbon dioxide, acetate, ketones, and long chain fatty acids.[3] Previous studies of the effect of the MCT ketogenic diet in epileptic children have shown no effect of the diet on liver function tests, serum cholesterol, lipoproteins, or low density lipoproteins.[4] This is in contradistinction to the standard ketogenic diet where hyperlipidaemia has been described.[5] The ketogenic diet does increase the concentrations of the ketones, betahydroxybutyrate, and acetoacetate without any change in the blood pH.[5] One of the final common pathways for the production of fatty change in the liver is the accumulation of excess hydrogen ion within the cell.[6] It is possible that the mechanism of fatty infiltration that we describe is due to a fall in the intracellular pH secondary to the chronic ketosis produced while on the diet.

Despite the fatty infiltration noted in our patients there was no noticeable effect on the liver function tests of these children, and more importantly when the diet was discontinued the abnormal changes disappeared. We report these changes so that clinicians using this diet may be aware of the abnormal abdominal ultrasound findings and their importance.

We would like to thank Dr WI Forsythe for permission to study the patients under his care

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HIV infection in Zimbabwe

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SUMMARY A total of 188 children with positive serology for HIV were identified during an 18 month period. Two seronegative children with clinical features of AIDS had seropositive mothers. Ten children were asymptomatic on initial testing; one has since died with infection. The commonest presenting features were generalised lymphadenopathy failure to thrive, chronic diarrhoea, and pneumonia Thirty four children are known to have died.

AIDS is reported to be endemic in parts of Africa and is thought to be largely heterosexually transmitted.[1] The vertical transmission of this disease to the children of mothers who are seropositive is now well recognised.[2 3] During 1985 patients began to present in Zimbabwe with illnesses suggestive of HIV infection. Young adults were presenting with severe herpes zoster, generalised lymphadenopathy, and severe respiratory infections. Children were seen who appeared to be suffering from malnutrition but whose socioeconomic histories were inconsistent with this, and they were failing to respond to standard nutritional and medical treatment. Other children were seen with recurrent infections or infections that were resistant to conventional treatment, suggesting an immunodeficiency state. Routine testing of donated blood began in August 1985 at the Harare Blood Transfusion Service and HIV testing has been available to clinicians since then.

Patients and methods

The Harare Blood Transfusion Service serves the northern half of Zimbabwe, covering a population in excess of three million. HIV testing was performed using the ELISA test,[4] and confirmation of all positive results was obtained using the Western blot technique.[5] All HIV request forms on seropositive children between October 1985 and March 1987 were reviewed. This accounts for all positive HIV serology in children documented in the north and eastern part of the country as no other facility was testing at the time. Clinical data was obtained from a questionnaire incorporated into the request form and additional information, when available, was extracted from some case notes in the central hospitals. The questionnaire was introduced only in the second half of the period under review and the quantity and quality of the information supplied was quite variable. In view of this the data represent only minimal estimates of each feature.

Results

A total of 188 children were found to be seropositive and of these 145 were identified in the central hospitals in Harare. Two other children who had clinical features suggestive of AIDS but negative serology and whose mothers were seropositive are included in the data.

CLINICAL FEATURES

The age distribution of the seropositive children at diagnosis is shown in the figure; 145 (77%) were identified before the age of 2 years. The commonest clinical features encountered are given in the table Recurrent infections included respiratory and gastrointestinal infections and one child developed bacterial meningitis. Diffuse nodular shadowing on the chest radiograph was reported in 14 (7·7%) and thrombocytopenia, neutropenia, or lymphopenia in six (3·3%). Encephalopathy was noted in one child. The asymptomatic children were all tested because either a sibling or a parent had been found to be seropositive.

As virtually all Zimbabwean babies are breast fed it is unlikely that more than one or two children in this review would not have received breast milk. This would only occur as a result of the death of the mother or total failure of lactation, which is extremely unusual

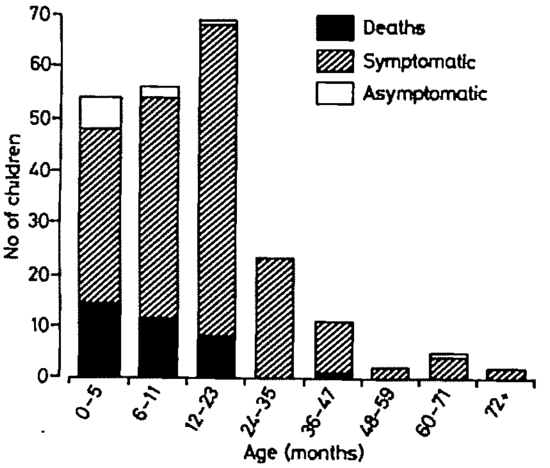

Figure *Age distribution of symptomatic and asymptomatic seropositive children at diagnosis and death*

Table *Clinical features in 181 children with symptomatic HIV infection*

	No (%) of children
Generalised lymphadenopathy	117 (64·6)
Failure to thrive	97 (53·6)
Abnormal chest radiograph	85 (46·9)
Pneumonia	75 (41·4)
Recurrent infections	74 (40·9)
Hepatosplenomegaly	57 (31·5)
Chronic diarrhoea	46 (25·4)
Oral candidiasis	33 (18·2)
Chronic parotid swelling	8 (4·4)
Kaposi's sarcoma	2 (1·1)

About 70% of Zimbabwean women deliver their children at home and therefore birth weight is often not recorded All children who attend clinics or hospitals in Zimbabwe, however, receive a child health card on which is recorded successive weight measurements. Most of the children in this study had received at least one live vaccine as BCG is normally given at birth or at the first visit to a clinic and polio vaccine is given with diphtheria, tetanus, pertussis vaccine for the first time at 3 months. There was only one documented adverse live vaccine reaction: this was a measles like illness that developed a week after the measles vaccine had been given. The child died with upper airway obstruction due to laryngotracheobronchitis and bronchopneumonia.

SERONEGATIVE CHILDREN

One of the seronegative children died within an hour of admission with gross marasmus and dehydration and his mother was found to be seropositive. The other seronegative child was severely marasmic with chronic diarrhoea that was unresponsive to standard treatment His mother was also found to be seropositive.

HIV STATUS OF PARENTS

Parents of seropositive children were tested where possible. Altogether 113 mothers were tested and 110 were seropositive. Three children with mothers who were seronegative had received blood products for sickle cell anaemia or haemophilia and this was presumed to be the source of the HIV infection. Thirty seven fathers were tested and 34 were seropositive. Two of the seropositive mothers with husbands who were seronegative had received blood transfusions which may have been the source of their HIV infection. Seropositivity in blood donors in 1985 was about 2%.

Twenty one of the parents were symptomatic with lymphadenopathy, herpes zoster, or weight loss. Three mothers died with clinical features of AIDS and positive serology and three fathers had died before presentation of the child, after prolonged illnesses associated with weight loss and chronic diarrhoea or lung disease.

DEATHS

Thirty four of the 190 children are known to have died in the central hospitals or soon after discharge. The age distribution at death of the 34 children is shown in the figure; the mean age at death was 10 months (range 1–36). Twelve children died during their first admission and in all but one the diagnosis was made on that admission. The remaining child had been asymptomatic three months previously when her twin had died and both were found to be seropositive.

Discussion

The clinical manifestations of HIV infection in Zimbabwean children do not differ appreciably from those described elsewhere.[2 3] The only way in which the findings of this report differ from reports from the West is the documentation of only one encephalopathic patient. This may, however, simply reflect failure to recognise the HIV infection in children with apparent primary encephalopathy. In the absence of specific tests of immune function it is possible that some of the children were asymptomatic HIV carriers, although most showed a characteristic feature such as generalised lymphadenopathy or severe, unresponsive infection. The asymptomatic children with positive serology under 1 year may have simply reflected passive maternal antibody transfer although one of these, the twin mentioned above, subsequently died with a severe respiratory infection.

AIDS in children is an increasing problem in Africa and elsewhere, and in the poorer countries the clinical manifestations can be easily mistaken for those of malnutrition and its associated immunodeficiency state. A large proportion of the children identified in this study were seen at the central hospitals in Harare where awareness of the disease was rapidly developing. It is likely, however, that many cases at rural hospitals were not diagnosed owing to lack of awareness of the growing epidemic.

The long incubation period of this condition is shown by the children who were identified only after the age of 5 years and raises the possibility that many school age children may yet develop symptoms. Seronegativity in children with advanced AIDS has been noted by previous authors[5] and draws attention to the importance of checking maternal serology in children who are immunologically impaired but have negative serology.

The spread of HIV infection has very serious implications in terms of human suffering, health expenditure, and the development of counselling services for affected families. A clarification of the part played by breast feeding in the transmission of the disease is important.[6] While failure to breast feed in developing countries may lead to infant death from other causes, women who are asymptomatic HIV carriers need to know the measures which will increase the chance of survival of their children, particularly in societies where the stability of marriage depends on fertility and the survival of children.

My thanks to John de Louvois and Ilya Kovar for their helpful comments on the manuscript

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Atypical presentation of subacute thyroiditis

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SUMMARY Subacute thyroiditis is extremely rare during the first decade of life. We describe a case of subacute thyroiditis in a 2 year old child whose initial clinical, sonographic, and radioisotopic features were indistinguishable from acute suppurative thyroiditis. The diagnosis was established by a raised antibody titre against adenovirus and typical increased thyroid function tests.

Subacute thyroiditis is a spontaneously remitting inflammatory disease of the thyroid gland that is probably caused by a viral infection.[1-3] Its incidence during the first decade of life is extremely rare. The youngest reported case was 3 years old.[1] The clinical distinction between acute suppurative and subacute thyroiditis is usually straightforward [2] The following case report describes a 2 year old girl with subacute thyroiditis and clinical presentation of acute suppurative thyroiditis.

Case report

A previously healthy 2 year old girl presented with a history of fever and pharyngitis 10 days before admission. Phenoxymethylpenicillin 200 000 units four times a day was prescribed. She was admitted to our hospital because fever persisted. On physical examination the child appeared ill. Her rectal temperature was 40·2°C. The neck was supple and there was mild cervical lymphadenopathy. There was a diffuse, firm, warm, erythematous swelling 3×5 cm in the anterior part of her neck affecting the left lobe of the thyroid gland, without fluctuation.

Haemoglobin concentration was 105 g/l with normal indices. The white cell count was $21\cdot5\times10^9$/l, with 82% polymorphonuclear cells, 1% band forms, and 17% lymphocytes. The erythrocyte sedimentation rate was 108 mm in the first hour Urinalysis gave normal results. Blood, urine, and throat cultures gave negative results. Serologic studies for antistreptolysin-O titre and a slide test for heterophile antibody of infectious mononucleosis also gave negative results. Her serum thyroxine concentration, measured by radioimmunoassay, was 257·4 nmol/l; triiodothyronine in vitro uptake, 85%; serum thyroid stimulating hormone, 1·5 mU/l; and free thyroxine index was greater than 38·6 pmol/l. No antithyroid microsomal and thyroglobulin antibodies were detected.

Ultrasound examination of the thyroid gland showed a diffuse enlargement of the left lobe (2·5×2·5×5 cm) without evidence of abscess formation. The right lobe appeared normal (0·5×1 cm). A ^{99m}Tc pertechnetate scan of the thyroid gland showed an enlarged left lobe without absorption of the isotope (figure) and a ^{67}Gallium scan showed increased absorption of the isotope in the area of the left lobe. The presumptive diagnosis was acute suppurative thyroiditis and intravenous benzylpenicillin (200 000 units/kg body weight/day) and cloxacillin (150 mg/kg body weight/day) were started. Her temperature fluctuated around 40°C for six days and then gradually returned to normal. Abscess formation was not shown on two subsequent ultrasound examinations. Recurrent fever persisted intermittently for two months. During that time the thyroid function tests were consistent with an euthyroid state and the left lobe of the thyroid gland

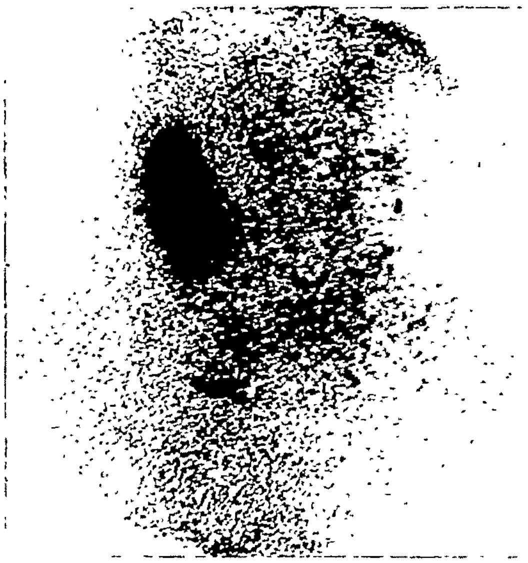

Figure *^{99m}Tc pertechnetate scan of thyroid gland two days after admission the left lobe is enlarged without absorption of the isotope* returned to normal size. The right lobe, however, enlarged to 2 cm×4 cm, without acute inflammatory signs. Another ^{99m}Tc pertechnetate scan still showed decreased absorption over the left lobe with normal absorption over the right lobe except for its upper portion. Over the next two months the thyroid function tests were consistent with hypothyroidism (serum thyroxine concentration, 11·6 nmol/l and thyroid stimulating hormone, 60 mU/l). Virologic studies showed a raised antibody titre against adenovirus (by complement fixation test) from less than 1:10 on admission to 1:120 six weeks later, without change in the antibody titre against other viruses. The patient was asymptomatic during the next 23 months, but the thyroid function test remained hypothyroid for 20 months and then returned to normal.

Discussion

This case illustrates the clinical dilemma when one faces a febrile patient with a unilateral, acutely enlarged, red, and tender thyroid gland. As treatment differs considerably between acute suppurative and subacute thyroiditis, the differential diagnosis is of paramount importance. Bacterial infection of the thyroid gland is rare in all age groups, but more common among children and young adults.[2 3] By contrast, most patients with subacute thyroiditis are at the third to fifth decade of life, although single case reports during the first decade of life have been published.[1 4] Most patients experience an insidious onset characterised by malaise, fatigue, and weight loss that may precede the symptoms and signs of thyroiditis, which might be unilateral in up to 20–33% of cases.[1 2] Hyperthyroidism is common during the initial phase of the disease and is usually followed by a hypothyroid state and eventual recovery.[1 5]

The age and the clinical presentation of our patient suggested the diagnosis of acute suppurative thyroiditis. Both the initial ultrasound and the radioisotope scans were consistent with the diagnosis, as described by Clair *et al.*[6] Two features, however, could retrospectively suggest that this was not the case: the lack of abscess formation and the impaired thyroid function tests. The migration of the inflammatory process to the opposite lobe is also characteristic of subacute thyroiditis.[1 2] The increased antibody titre against adenovirus (from less than 1:10 to 1:120) suggests that adenovirus infection was associated with the subacute thyroiditis in this case. It must be stressed that direct evidence of viral etiology in this disorder has only rarely been obtained.[2]

This case shows the necessity to consider the possibility of subacute thyroiditis in young children even if the clinical, ultrasonographic, and radioisotopic features resemble acute suppurative thyroiditis. Impaired thyroid function tests, lack of abscess formation, and rising titre against a specific virus may serve to distinguish between these conditions.

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Sweat tests and flucloxacillin

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SUMMARY Sweat tests were carried out on 14 patients with cystic fibrosis and 14 controls when on no antibiotics and when taking oral flucloxacillin. No significant differences in results were obtained for either group whether on or off antibiotics. Oral flucloxacillin does not affect sweat electrolytes and is not a contraindication to sweat testing

The sweat test remains the definitive test for diagnosis of cystic fibrosis. It has been reported, however, that normal concentrations of sweat chloride have been obtained in the presence of abnormally high concentrations of sweat sodium in a patient with cystic fibrosis while taking oral cloxacillin,[1] thus causing considerable delay in making the diagnosis.

When reviewing the methodology and diagnostic accuracy of sweat tests in our hospital we have become aware that oral flucloxacillin has occasionally been used as a contraindication to sweat testing of patients where the diagnosis of cystic fibrosis has been raised, sometimes resulting in a long delay in diagnosis and, potentially, a poorer prognosis.[2-4] As this is a clinical situation where antistaphylococcal antibiotics are often used, we felt it important to carry out a study to determine whether reliable sweat test results can be obtained in subjects taking oral flucloxacillin.

Subjects and methods

Sweat tests, using the quantitative method of Gibson and Cooke,[5] were performed on 14 patients with cystic fibrosis (age range 2–17 years; mean 9·14 years) and 14 control subjects (age range 3 months to 19 years; mean 7·57 years). Control subjects comprised normal siblings of patients with cystic fibrosis, other hospital inpatients, some of whom had previously had normal sweat tests as part of their investigations, and healthy volunteers.

All sweat tests were performed and analysed in the same laboratory by trained laboratory staff. Each subject had two sweat tests; one while on no antibiotics and another after the subject had been taking oral flucloxacillin for at least 48 hours. All patients with cystic fibrosis (except one with adequate pancreatic function) were also taking pancreatic extracts and vitamin supplements All control subjects were on no other medication.

In all tests the sweat rate was either greater than 1g/m^2/minute or weight greater than 100 mg of sweat. Sodium concentration was measured by flame photometry and chloride concentration by a coulometric method.

Results

Results of sweat tests performed while subjects were not taking flucloxacillin show a clear demarcation between controls and patients with cystic fibrosis when both sodium and chloride are considered (figure). All control subjects had chloride concentrations less than 70 mmol/l. Two patients, however, had sodium concentrations higher than 60 mmol/l, but chloride concentrations were lower than sodium and were within the normal range. Both these subjects were in the older age group (age 14 and 16 years) and neither showed any symptoms or signs suggestive of the diagnosis of cystic fibrosis. All cystic fibrosis patients had concentrations in the

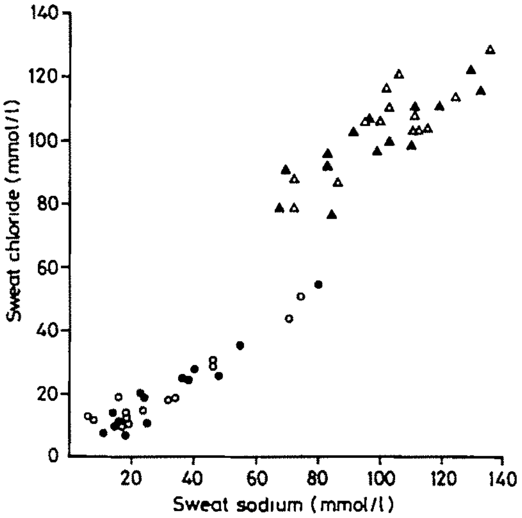

Figure *Sweat test results in controls and patients with cystic fibrosis while on and off oral flucloxacillin Controls no flucloxacillin (○), on oral flucloxacillin (●); patients with cystic fibrosis no flucloxacillin (△), on oral flucloxacillin (▲).*

abnormal range, (sodium greater than 60 mmol/l, chloride greater than 70 mmol/l).

Results of sweat tests performed while subjects were taking oral flucloxacillin also showed a clear demarcation between the two groups (figure). There was no significant difference between the two sets of results—that is, on and off flucloxacillin (Wilcoxon signed rank test:p>0·5) in either group

Discussion

It has been suggested that substitution of the chloride ion by cloxacillin may occur and artefactually produce unusually low sweat chloride results[1] causing difficulty in confirming the diagnosis of cystic fibrosis. Our study disproves this hypothesis and confirms that there is no contraindication to sweat testing while a subject is taking oral flucloxacillin.

The possibility that the artefactually low chloride results were due to analytical interference exists as our method differs from that (modified Schales and Schales) used by Griffiths. We would, however, reiterate that sweat tests should be performed by experienced laboratory staff with measurement of both sodium and chloride ions. Results must always be considered in the light of clinical findings as well as the age of the patient to avoid misdiagnosis of cystic fibrosis.

Further work is required to ensure that other commonly used antibiotics do not interfere with sweat test results.

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Mineral content of rib bone in infant deaths

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SUMMARY The mineral content of rib bone in infants who died unexpectedly was similar to that among those who died after acute illnesses, and it was significantly associated with both crown to heel length and age. In those dying from chronic illnesses it was lower than in the other two groups.

Unexplained death in infancy is thought to be caused by more than one disease. The process that results in some cot deaths may be active for a considerable time beforehand: infants may not gain weight properly before death,[1] and retardation of growth of the costochondral junction has been shown histologically in specimens taken at necropsy from such infants [2] We used single photon absorptiometry to measure the mineral content of the ribs near the costochondral junction to find out if histological changes in cartilage at necropsy are associated with reduced mineral content of the ribs in these infants.

Patients and methods

We studied 92 consecutive necropsies undertaken in children under the age of 2 at the Children's Hospital, Sheffield between October 1985 and February 1987. Details recorded included age at death in days (corrected for prematurity), sex, crown to heel length, and weight. They were divided into three groups according to type of diagnosis; unexplained death (n=62), death after a sudden acute illness in a previously well child (n=18), and death after a chronic illness (n=12).

In all cases specimens of the right fifth rib including the costochondral junction were taken and stored and transported in a buffered calcium formalin solution to prevent deterioration of the mineral content. Single photon absorptiometry was carried out as previously described.[3] Each rib was scanned 1·5 cm from the costochondral junction unless it was shorter than that, when it was scanned at its midpoint. As each rib specimen was ellipsoidal, it was measured at its widest point with calipers. For each rib, the mineral content was divided by its width to provide a size-corrected measure of the mineral content of the bone.

Results

Fig 1 shows a scattergram of the mineral content of rib against crown to heel length for all cases. Fig 2 shows regression lines of the mineral content of ribs plotted against crown to heel length for the three groups. The mean mineral content of the bone in the group of unexplained deaths was 2·11×crown to heel length −53·29, in the group who died after acute illnesses it was 2·58×crown to heel length −82·22, and in the group who died after chronic illnesses it was 1·28×crown to heel length −20·96.

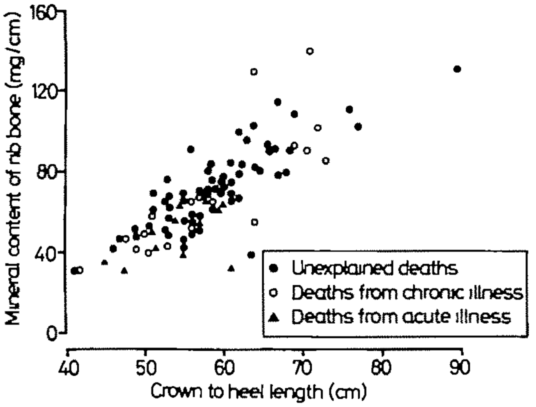

Fig 1 *Scattergram of mineral content of rib bone and crown to heel length for individual infants.*

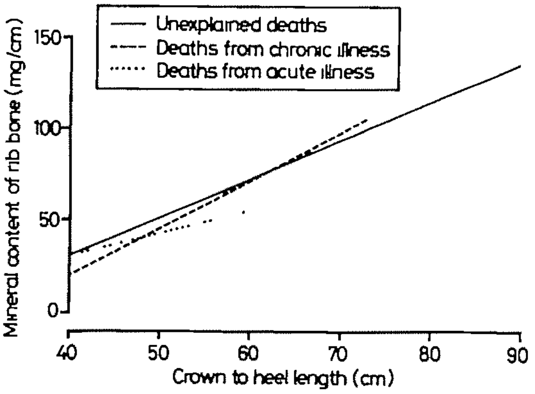

Fig 2 *Regression lines for mineral content of rib bone and crown to heel length for the group who died unexpectedly*

Nearly three quarters of the 62 unexplained deaths (72%) occurred in boys. Thirty five per cent were below the 10th centile for weight. The mineral content of the bone correlated significantly with age ($r=0·761$, $p<0·001$) but more closely with crown to heel length ($r=0·816$, $p<0·001$; fig 2) The mean mineral content of bone/width was 10·40 mg/cm^2 and this proportion did not alter with age.

Just over half of the 18 who died of acute illness (56%) were boys and 12 (67%) were below the 10th centile for weight. Mineral content of bone correlated significantly with age ($r=0·725$, $p<0·001$) but more closely with crown to heel length ($r=0·814$, $p<0·001$; fig 2) The mean mineral content of bone/width was 10·73 mg/cm^2.

Five of the 12 infants who died of chronic illnesses (42%) were below the 10th centile for weight. There was poor correlation between mineral content of bone and age ($r=0·20$, $p>0·5$) and between mineral content of bone and crown to heel length ($r=0·50$, $p<0·1$). These infants had a lower mean mineral content when compared with other infants of similar crown to heel length (paired *t* test on 12 matched pairs; $p<0·01$). The mean mineral content of bone/width was 7·69 mg/cm.^{2}

Discussion

There was an unusually high proportion of unexplained deaths in this series because necropsies on all children dying at home in South Yorkshire are carried out at the Children's Hospital, Sheffield.

In all three groups crown to heel length provided a better correlation with mineral content of bone than age, but crown to heel length and mineral content of bone are both measures of skeletal growth rather than of age. In both the group who died of acute illnesses and the group of unexplained deaths the regression lines for mineral content of bone against age, and mineral content of bone against crown to heel length, lay close to one another (fig 2). These must be interpreted with caution, however, because two thirds of the infants who died of acute illnesses weighed below the 10th centile at the time of death. This might represent either acute weight loss during the terminal illness or indicate otherwise unsuspected illness

With the above proviso we could find no evidence of decreased mineral content in the ribs in infants dying unexpectedly compared with those dying from acute serious illnesses. This was confirmed by the similar mean values of mineral content of bone/

width of rib in the two groups. The results indicate that disturbances in the formation of cartilage seen by others are not longstanding enough or severe enough to cause a measurable reduction in the mineral content of ribs in a study of this size. Reduced mineral content in ribs of infants dying of chronic illnesses was expected as studies in the neonates have shown that undernutrition (relative to the nutrition provided by the placenta when it is functioning correctly) may result in pronounced reductions in the mineral content of bone.[4]

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Functional residual capacity related to hepatic disease

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SUMMARY Functional residual capacity was measured in 20 children (aged 3·1–11·2 years) with liver disease. Children with severe liver disease regardless of diagnosis, had reduced functional residual capacities (<80% of expected). Children with α−1 antitrypsin deficiency had higher functional residual capacities than those with other hepatic diagnoses. Three children had a functional residual capacity >120% of expected, all had α−1 antitrypsin deficiency

In childhood α−1 antitrypsin deficiency is usually associated with liver disease, but it has been suggested that asthma and bronchitis may be commoner in children over 8 years of age with α−1 antitrypsin deficiency.[1] No respiratory measurements, however, were performed and the authors were unable to comment whether the symptoms were early manifestations of emphysema.[1]

Recently it has become possible to measure functional residual capacity by helium gas dilution reproducibly and accurately even in children as young as 2 years of age.[2 3] The aim of the present study, using this technique,[2 3] was to determine if abnormalities of functional residual capacity were present in young children with α−1 antitrypsin deficiency. Secondly, by comparing their results with those of children with other hepatic diagnosis, we aimed to determine whether the abnormalities specifically related to α−1 antitrypsin deficiency rather than a non-specific effect of hepatic disease

Patients and methods

Twenty children attending the paediatric liver service at King's College Hospital were studied. Only one child, who had previously been diagnosed as suffering from asthma, had respiratory symptoms. Twelve children suffered from α−1 antitrypsin deficiency (five boys and seven girls, median age 5 years (range 3·1–11·5 years)). Eight other children were also studied: five with biliary atresia, two who had had neonatal hepatitis, and one with congenital hepatic fibrosis. This latter group, who were designated controls, consisted of three boys and five girls with a median age 4·5 years (range 3·5–8·6 years). The children in both groups were classified into four subgroups according to disease severity (figure).

Ethical permission for the study was granted by King's College Hospital ethical committee and parental consent was obtained.

All children had their functional residual capacity measured by helium gas dilution using a water sealed spirometer (Gould Pulmonet 3) in the paediatric respiratory laboratory.[2 3] All recordings were coded and then analysed blind of the child's clinical details. Each child's results were compared with published normal data[2] or data collected from 60 healthy children of similar ages to the study population. Functional residual capacity was ex-

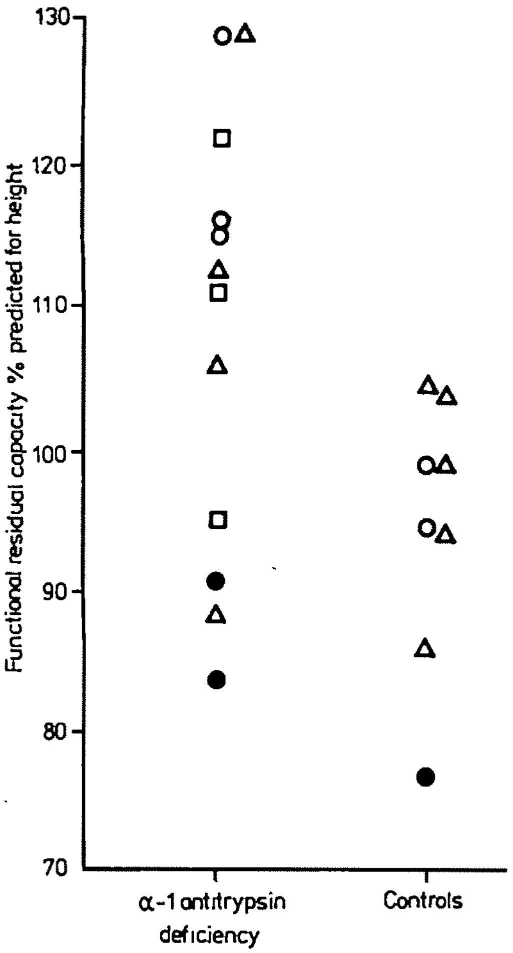

Figure *Functional residual capacity is expressed as a percentage of that predicted for height in the children suffering from α−1 antitrypsin deficiency (left) and with other hepatic diagnoses (controls) (right) Each child is depicted according to the severity of liver disease* ○*=no clinical or biochemical evidence of liver disease at the time of measurement (subgroup 0),* □*=mildly abnormal liver function tests but no abnormal clinical signs (subgoup 1),* △*=abnormal liver function tests, enlarged liver or spleen, or both (subgroup 2), and* ●*=cirrhosis (proved on biopsy) with massive splenomegaly with or without ascites (subgroup 3)*

pressed as the percentage for height or age using these normal ranges. Children who had a functional residual capacity ≥120% of that predicted for height were remeasured 20 minutes after bronchodilator treatment (500 μg terbutaline) A change in functional residual capacity after the bronchodilator of greater than 8% was accepted as clinically important.[3]

To assess if α−1 antitrypsin deficiency had a different effect on lung function than other hepatic diagnoses the functional residual capacity of the two groups were compared. To assess the effect of disease severity on lung function the results of the four subgroups were compared.

To assess if differences in functional residual capacity between the groups reached significance the Wilcoxon rank sum test was used.

Results

The children with α−1 antitrypsin deficiency tended to have higher functional residual capacities related to both height ($p<0{\cdot}05$) and age (non-significant) (mean 113%, range 85–130% related to height and mean 104%, range 67–128% related to age) than those suffering from other hepatic diagnoses (mean 100%, 78–106% related to height and mean 86%, range 69–104% related to age). There was no significant difference in the children's height related to age between the two groups.

Only three children had significantly raised functional residual capacities (>120%), all had α−1 antitrypsin deficiency, but only one had severe liver disease (subgroup 2). Only one of the three showed a clinically important change in functional residual capacity after bronchodilator treatment; this child had previously been diagnosed as suffering from asthma. The other two, with functional residual capacities of 130% and 125% related to height, were 6·5 and 3·1 years old, respectively. Neither had chronic respiratory problems nor a positive family history. Both these children have subsequently been recalled and their functional residual capacities remain similarly raised.

Children with severe liver disease (subgroup 3 and some of subgroup 2) regardless of hepatic diagnosis tended to have lower functional residual capacities (see figure). All subgroup 3 had a functional residual capacity of less than 80% of that predicted for age, and this group had significantly lower lung volumes that the other three subgroups ($p<0{\cdot}01$). Although one child of subgroup 3 was on the 10th centile for height, the other two were on the 50th and 90th centiles respectively.

Discussion

Owing to the difficulty, until recently,[2 3] of performing respiratory function tests in young children, little has been known regarding the effect of hepatic disease and in particular α−1 antitrypsin deficiency on lung function. In a small number of children (seven) less than 8 years of age, Vance *et al* showed both an abnormality of forced expiratory flow rate and increased frequency dependency of total pulmonary resistance measured by forced oscillation[4] There is only one reference to a younger child with α−1 antitrypsin deficiency and respiratory disease.[5] This child first presented at 3 years of age with a six and a half year history of chronic pulmonary disease, emphysema was diagnosed by lung biopsy at 13 years of age. In the present study three children, all with α−1 antitrypsin deficiency, one as young as 3 years of age, had significantly raised lung volumes when related to both age and height. In two of these children this was unresponsive to bronchodilator treatment so these findings are highly suggestive of emphysematous changes. Neither child had severe liver disease, nor respiratory symptoms or signs.

In all children with severe liver disease, irrespective of diagnosis, low lung volumes were shown. This association was particularly noticeable when lung volumes were related to age. The children with severe liver disease, however, were not significantly smaller than the other children studied, indeed one was on the 90th centile for height The most likely explanation, therefore, for the association of severe hepatic disease and reduced lung volume is compression due to hepatosplenomegaly and ascites.

In conclusion, these results suggest that α−1 antitrypsin deficiency even in early childhood may be associated with emphysema, and that in severe liver disease lung volume is reduced. We now intend to follow all such children prospectively in an attempt to determine the exact incidence of respiratory abnormalities and their evolution with time.

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Melatonin state in Mendenhall's syndrome

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SUMMARY We report a case of Mendenhall's syndrome that presented as hypoglycaemia. The clinical and biochemical features of the case are described including, for the first time, studies of melatonin state showing raised melatonin metabolite excretion in the urine as might be expected with disordered pineal function.

A syndrome of dysmorphism, dental precocity, hirsutism, acanthosis nigricans, abdominal protuberance, phallic enlargement and insulin resistant diabetes mellitus was first described by Mendenhall in 1950.[1] Since then a number of similar cases have been recognised,[2] and in each of these diabetes mellitus has developed in mid childhood and the child has died of ketoacidosis, with the exception of one child in whom hypophysectomy was performed.[2] Pineal hyperplasia has been found at necropsy of all patients dying.[1–3] We describe a further case in which the presenting symptom was hypoglycaemia in the neonatal period.

Case report

A boy, weighing 2520 g, was born after an uneventful pregnancy at 44 weeks' gestation. It was the second pregnancy of healthy non-consanguinous parents. Abdominal distention and facial dysmorphism were noted at birth. The features included a coarse facies with a prominant jaw, large eyes and ears, fine downy hair over the body, and short stubby fingers. He was also noted to have a long penis with normal sized testes. At 10 hours of age the baby started to have seizures secondary to hypoglycaemia (blood glucose concentration <0·1 mmol/l) and intravenous dextrose was started The intravenous infusion was required for 48 hours because of recurrent hypoglycaemia but after its withdrawal his blood glucose remained normal. Plasma insulin concentrations were measured by radioimmunoassay and found to be very high (1680 mU/l). These were remeasured at 2 months of age and were again high at 2460 mU/l (with a blood glucose concentration of 6·6 mmol/l).

At 7 months of age a glucose tolerance test gave a normal result but he had persistently raised insulin concentrations. Chromatographic analysis of his serum showed peaks coeluting with proinsulin and insulin. High concentrations of insulin were further confirmed by bioassay. Glucose tolerance tests were performed and insulin concentrations were measured on both parents and gave normal results. The boy's glucagon and testosterone concentrations (taken randomly) at this time were modestly raised: glucagon 53 pmol/l (normal range <50 pmol/l) and testosterone 0·7 nmol/l (normal range 0·07–0·67 nmol/l for prepubertal boys).[4]

The child developed acanthosis nigricans of the neck and axilla at 1 year of age. Primary dentition started at 3 months and secondary dentition at 3 years. His intelligence quotient was assessed as normal (112 by the Stanford-Binet test at 3 years) Other problems included tonsillar/adenoidal hypertrophy leading to middle ear disease. At the age of 7 he developed the first signs of diabetes mellitus with mild ketonuria, and a glucose tolerance test gave a glucose concentration of 3·8 mmol/l fasting and 17·1 mmol/l two hours after the load. Hyperinsulinaemia persisted with concentrations varying from 439 mU/l (blood glucose 3·8 mmol/l) to 4255 mU/l (blood glucose 14·3 mmol/l). A computed tomogram performed at this time showed no evidence of pineal enlargement. Combined pituitary function testing was performed. A total of 0·3 unit/kg of soluble insulin was given intravenously but hypoglycaemia was not induced. Normal concentrations of growth hormone, prolactin, cortisol, luteinising hormone, follicle stimulating hormone, and thyroid stimulating hormone were obtained Random testosterone concentrations were measured on two further occasions and were 0·3 nmol/l and 0·8 nmol/l, respectively.

At 11 years of age he developed more pronounced glycosuria and symptoms of lethargy. A blood glucose profile over 24 hours showed his blood glucose varying between 5·4 mmol/l (fasting) and 12·5 mmol/l. This latter glucose concentration corresponded with a plasma insulin of 3300 mU/l and C peptide of 19·6 nmol/l showing grossly enhanced endogenous insulin secretion. (His glycosylated haemoglobin was 11·7%.) Carbohydrate spacing, guar gum, a high fibre diet, and tolbutamide were used in an attempt to control his diabetes but with only minor benefit, which was not sustained. He was therefore started on insulin but despite soluble insulin 50 units in the morning and 44 units in the evening there was no improvement.

Assays for serum melatonin and metabolites have recently been developed[5] and in view of the evidence for pineal hyperplasia it was clearly of interest to examine the patient's pineal hormone state. Urinary 6-sulphatoxymelatonin (aMT6s) measured over 24 hours was raised at 19·8 μg (8 am–2 pm, 3·51 μg; 2 pm–8 pm, 2·31 μg; 8 pm–2 am, 0·85 μg; and 2 am–8 am, 13·13 μg). The mean (SD) normal range obtained from analysing urine from 11 children of this age was 7·58 (2·65) μg/24 hours (C Bojkowski, unpublished data) Plasma melatonin concentrations were 26·1 pg/ml at 12 noon and 239·6 pg/ml at 12 midnight. Normal data for plasma melatonin concentrations are limited in children but a report by Waldhauser and Dietzel suggests that the night value for our patient is, at least, high normal.[6]

Discussion

The progression to diabetes mellitus in Mendenhall's syndrome has been well documented.[1-3] Various reasons for the insulin resistance have been advanced but there has never been any evidence for appreciable insulin antibody formation, hormonal antagonists to insulin, nor for secretion of abnormal insulin. Reduced numbers of insulin receptors have been shown in erythrocytes (Perez Corral F, de la Vina S, Carbo ME, *et al.* Rabson syndrome: models of insulin resistance due to decreased number and affinity of insulin receptors in erythrocytes [Abstract] *Diabetologia* 1980;**19**:36.), monocytes, and fibroblasts of patients with Mendenhall's syndrome.[2]

Our patient is the only child yet described to present with hypoglycaemia He appears to have had a normal response to high insulin concentrations in the neonatal period with progressive resistance to insulin activity developing over the subsequent years. This raises the question whether the underlying abnormality is one of hyperinsulinism with insulin resistance developing as a protective mechanism (at least initially).

Plasma melatonin was at least high normal in the midnight specimen and excretion of melatonin metabolites were clearly raised in our patient. This has not previously been documented but perhaps is not surprising given the evidence for pineal hyperplasia in Mendenhall's syndrome The features of the syndrome such as hirsutism and phallic enlargement, however, cannot be explained by excessive melatonin secretion per se as melatonin administration has not been shown to duplicate the functional effects of the pineal. It is possible that other, as yet undefined, pineal hormones or metabolites may be implicated in causing some of the features of the syndrome.

We thank Drs J Arendt and RW Logan for their help in the investigation of this patient

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Collodion babies with Gaucher's disease

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SUMMARY Two neonates with acute infantile cerebral Gaucher's disease had prominent collodion skin. Ichthyosis has been described in some cases of metabolic lipid disorders, however, this is the first report of the association of lamellar desquamation of the newborn (collodion baby) with Gaucher's disease.

Gaucher's disease is characterised by an abnormal accumulation of cerebrosides primarily in cells of the reticuloendothelial system. The disease is due to a deficient activity of lysosomal glucocerebrosidase and is transmitted as an autosomal recessive trait. It is a clinically heretogeneous disorder, however, with at least three recognised types. In the acute infantile cerebral form (type II) the baby appears normal at birth but soon exhibits neurological symptoms and hepatosplenomegaly. Death usually occurs in the first year of life. The skin is not pigmented in the acute infantile form. Collodion skin and ichthyosis are not recognised skin manifestations in any of the forms of Gaucher's disease.[1] We report two siblings with generalised ichthyosis associated with infantile Gaucher's disease.

Case reports

A 27 year old Lebanese woman was admitted to this hospital in September 1986 for her second confinement There was no consanguity with her Lebanese husband and there was no family history of Gaucher's disease or ichthyosis. Her first pregnancy in 1984 resulted in the delivery of a boy (case 1) in another hospital in Sydney.

Case 1. A 3500 g boy was delivered by caesarean section at 39 weeks' gestation. Generalised thick collodian like skin, gross hepatosplenomegaly, and apathy were noted at birth. The ichthyotic skin peeled over the next five days and there were no subsequent skin lesions. Soon after birth he had recurrent laryngospasms, generalised convulsions, and a persistent thrombocytopenia. Diagnosis of Gaucher's disease was established by leukocyte enzyme assays. He died at the age of 3 months after a respiratory arrest in hospital. The parents did not consent to a postmortem examination.

Case 2. The mother presented at 20 weeks' amenorrhoea but declined the offer of prenatal diagnosis. Polyhydramnios occurred in late gestation and a boy weighing 3400 g was delivered by caesarean section at 40 weeks' gestation. He was apnoeic at birth and remained dependent on assisted ventilation until death at 11 days of age. Generalised tight collodian like skin (figure), gross hepatosplenomegaly, and generalised joint contractures were noted. He was apathetic from birth and had frequent refractory convulsions and opisthotonos. The tight collodian like skin started to shed from the first day of life. At the time of death the hands, feet, and back were scaling in large sheets.

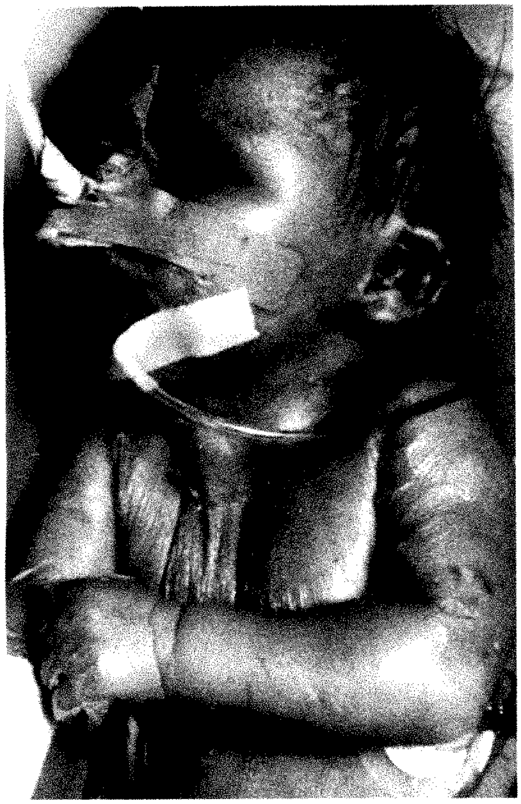

Figure *Case 2 at 3 days old showing desquamation of collodion skin.*

Results of laboratory investigations showed a persistent thrombocytopenia with platelets in the range 19–35×10^9/l and a mild conjugated hyperbilirubinaemia. His liver enzymes were normal but acid phosphatase was raised (28 U/l, normal 5·4 U/l). White cell enzymes measured (in pmol/minute/mg protein) showed deficiencies consistent with Gaucher's disease. The β-glucocerebrosidase was 35 pmol/minute/mg protein (normal range 600–3200), β-glucosidase was 17·1 pmol/minute/mg protein (normal range 60–220).

At postmortem examination Gaucher cells were found in lymph nodes, thymus, liver, spleen, adrenals, and bone marrow. The brain also showed changes consistent with cerebral Gaucher's disease. Section of skin of the back showed hyperkeratosis with follicular plugging. The underlying epidermis and dermis appeared normal. The skin was fixed in Millonig's buffered formalin and processed for transmission electron microscopy. The keratinocytes showed normal maturation and no abnormal storage products were seen. The keratinised layer was thick but otherwise normal. The granular layer was considerably reduced in thickness.

In January 1987 the parents returned for follow up counselling. The mother reported that she was pregnant at 11 weeks' amenorrhoea. A prenatal diagnosis by chorionic villi biopsy was performed, and this was followed by a first trimester abortion as the fetus was affected with Gaucher's disease.

Discussion

A striking clinical feature in these two infants was generalised collodion skin. Although scaling disorders have long been attributed to abnormalities of keratin protein, there has been increased awareness of the relation between ichthyosis and specific lipid metabolic disorders. A few examples include X linked ichthyosis with steroid sulphatase deficiency,[2] neutral lipid storage disease,[3] and Refsum's disease.[4]

Elias emphasised the importance of lipids in the integrity of the stratum corneum based on evidence from morphological studies by freeze fracture imaging and by histochemical and cytochemical studies.[5] He suggested abnormal lipid composition would affect the normal cohesion and orderly dissolution of corneocytes, which would be the basis of scaling skin disorders. In our infants the delicate balance of stratum corneum lipid composition may have been disturbed as a direct effect of the lipoidosis, resulting in the collodion membrane. As in the two cases we report, authors reporting other lipid diseases have not described any obvious abnormal storage products seen in ultrastructural examination of the ichthyotic skin that is associated with these diseases.[2-4] An alternative suggestion is that the ichthyosis and lipid disorder may represent allelic disorders with different mutations in the structure gene for the enzyme.[6] The range of clinical presentation including collodion baby in these two cases may be due to a single mutation at the glucocerebrosidase locus. Furthermore, it is also possible that the hyperkeratosis and glucocerebrosidase deficiency were two closely linked genetic conditions and that these two infants represented a variant of Gaucher's disease with neurocutaneous manifestations.

We thank Dr Andrew Berry of the Royal Alexandra Hospital for Children, Sydney, in providing information of the first reported case.

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'At first the full reaction may be delaye may be a period of numbness or blunting in which bereaved person acts as if nothing had happened for a few hours or days or up to two weeks. Thereafter attacks of yearning and distress with autonomic disturbance begins. These occur in waves and are aggravated by reminders of the deceased. Between the attacks the bereaved person is depressed and apathetic with a sense of futility. Associated symptoms are insomnia, anorexia, restlessness, irritability with occasional outbursts of anger directed against others or the self, and preoccupation with thoughts of the deceased.'[1]

My study of perinatal bereavement stems from a prior interest in the emotional and psychological aspects that accompany illness in children and its impact on the family. To help me deal with these problems I sought help by joining a Balint Group on the doctor–patient relationship; and later we—a group of like minded paediatricians—started the Anna Freud Paediatric Study Group which lasted for some 20 years until her death. This led to the establishment of my 'Tuesday' clinic in Woolwich where every type of emotional problem associated with illness was tackled: chronic illness, handicapped children, life threatening illnesses, and bereavement.

The bereavement clinic

In the late 1960s when Machin approached us to participate in the South East Metropolitan Region study of spontaneous aborted fetuses I invited parents who had suffered a perinatal bereavement at the British Hospital for Mothers and Babies to talk things over.[2] There were at that time no guidelines from others experienced in the field and no literature that I could find on the subject. But interestingly enough this 'experimental bereavement clinic' coincided with publication of some papers on the subject, which demonstrated a new climate of thinking.[3-5] This motivated me to try to engage

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rent initiatives led to
and Neonatal Death S
London) and publications
Midwives[8] and the Royal Colle
and Gynaecologists.[9] A remarka
occurred in the last 15 years, as is e
perennial spate of articles in pop
newspapers, and especially the two e
produced by Esther Rantzen for the
'*The Lost Babies*'.

To answer the particular needs of
increasing number of families whose
fetus is being diagnosed by ultrasound, the
group, Support after Termination for Ab
Pregnancy (SATFA) has been launched. Bat
written on the management of 12 to 28 w
loss.[10]

What and how

What are the basic and fundamental le
have learnt from all this experience in th
ment of perinatal bereavement? Essentially
a painful, difficult, and demanding task and
much patience and applied endeavour. I lea
very quickly that the medical model of 'pain rel
and 'tea and sympathy' does not meet the needs of bereaved families. The pain of the death of a baby cannot be extinguished. It has to be lived through. Experience of those working in the field of bereavement has taught us that grief is the inevitable emotional reaction to loss and that mourning is the psychological process that gradually undoes the psychological bonds with the dead child and eventual freedom from the preoccupation with the dead baby. Adequate mourning enables the bereaved to readjust and to organise their lives successfully.

decline in mortality from chronic bronchitis over the past 50 years.

Another close geographical relation in England and Wales is that between current mortality from stroke and maternal mortality from causes other than puerperal fever in the early years of the century.[11] Toxaemia was the commonest cause of these maternal deaths. Hypertension may be the mechanism linking maternal health and risk of stroke in the offspring. Maternal hypertension increases the risk of hypertension in the children,[12] and hypertension is a risk factor for stroke. There is increasing evidence that hypertension originates in childhood [13] 'Tracking' of blood pressure has been repeatedly observed in longitudinal studies of children and adults.[14–17] A link between the intrauterine environment and hypertension is suggested by the negative relation between birth weight and blood pressure at age 36 in the 1946 cohort.[18] The distribution of stroke in Britain may therefore reflect the past distribution of poor living standards which accompanied industrialisation or economic depression in certain areas These adversely affected the development of girls and increased the risk of stroke in their offspring, possibly through mechanisms associated with blood pressure and rates of growth in early life.[11]

The geographical distribution of ischaemic heart disease in Britain is similar to that of stroke. A study in 24 British towns has shown that the mean blood pressure of adult men in a town correlates with the prevalence of ischaemic heart disease.[19] Childhood influences associated with blood pressure could determine the distribution of both diseases. Their time-trends, however, are opposite. Mortality from stroke has fallen in Britain over the past 40 years, which is consistent with past improvements in maternal health and physique. Ischaemic heart disease mortality, however, has risen steeply This is attributed to increasing affluence, in particular diet, during adult life. Ischaemic heart disease may therefore have two groups of causes. One acting through the mother or in infancy, which is associated with poor living standards.[20] The other acting in adult life, which is associated with affluence. Further evidence for the existence of the former comes from the inverse relation between ischaemic heart disease and height, which is largely determined by growth in childhood [21] Longterm 'programming' of lipid metabolism during infancy, as a result of infant feeding, is a mechanism for which there is increasing evidence in experimental animals, and which may be a link between childhood and the risk of ischaemic heart disease.[22]

A prediction from this is that the improvements in maternal and child health in generations born before the second world war will now be reflected in a fall in ischaemic heart disease Rates are beginning to fall in many parts of Britain and there have already been substantial falls in the United States, Canada, Australia, and New Zealand.

Epidemiological investigation of the effect of childhood influences on the risk of cardiovascular disease and chronic bronchitis is being pursued in a variety of ways – through prospective and retrospective studies of individuals, detailed analyses of time-trends and studies of migrants. If they show major effects we will need a new national strategy for reducing inequalities of health in Britain.[1] The current strategy is focused on adult lifestyles. The new one will need to address differences in the development and health of children.

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Current topic

Childhood causes of adult diseases

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The search for influences in the adult environment which determine the risk of the major non-malignant diseases, cardiovascular disease, and chronic bronchitis has met with limited success. Cigarette smoking has been implicated; evidence on dietary fat has accumulated to the point where a public health policy of reduced intake is considered prudent, even if the case is not proven. Much, however, remains unexplained.

A puzzling aspect of the epidemiology of ischaemic heart disease, stroke, and chronic bronchitis in Britain is that they are more common in poorer areas and in lower income groups[1] Differences are large, greater than twofold For ischaemic heart disease they are also paradoxical in that its steep rise in Britain and elsewhere has been associated with rising prosperity. Why should its rates be lowest in the most prosperous places, such as London and the home counties? Variations in cigarette smoking and adult diet do not explain these differences.

There is increasing evidence that they result from geographical and social class differences in child development and health 60 and more years ago. Past differences in child health were reflected in the wide range of infant mortality. For example in 1921–5 infant mortality ranged from 44 per 1000 births in rural West Sussex to 114 in Burnley The highest rates were generally in northern counties where large manufacturing towns had grown up around the coal seams. Rates were also high in poor rural areas such as north Wales. They were lowest in counties in the south and east, which have the best agricultural land and are historically the wealthiest. A series of government inquiries on child and maternal mortality from 1910 onwards, prompted by revelations of the poor physique of military recruits, showed how these differences in infant mortality were related to differences in maternal physique and health, infant feeding, housing, and overcrowding.[2–4]

Mortality statistics for England and Wales can be used to compare the present distribution of adult death rates from specific causes with the past geographical distribution of causes of infant mortality. These comparisons can be made with the country divided into large towns and groupings of small towns and rural areas within counties, totalling 212 areas—a division of the country used in routine statistics since the turn of the century.

Mortality from chronic bronchitis and emphysema is concentrated in the large towns. Its geographical distribution correlates remarkably closely with infant mortality from bronchitis and pneumonia in the early years of the century[5] The coefficient of correlation is 0·85. A similarly high coefficient is seen for each sex separately and if comparisons are made between large towns only, or small towns or rural areas.

Suspicion that respiratory infection in early childhood might be a major cause of chronic bronchitis in adult life has been reinforced by follow up studies which show that after bronchiolitis, bronchitis, or pneumonia abnormalities of pulmonary function may persist through childhood.[6–9] In the national sample of children born in Britain during 1946 there was a strong association between the occurrence of one or more lower respiratory infections before 2 years of age and the prevalence of cough during the day, or at night in the winter, at the age of 25 years.[10]

The close geographical relation between infant mortality from respiratory infection and adult mortality from bronchitis may be interpreted as strong evidence for a direct causal link between respiratory infection in early childhood and chronic bronchitis. Regression analysis of bronchitis and lung cancer mortality suggests that childhood infection is more important than cigarette smoking in determining the prevalence of bronchitis.[5] The high rates of chronic bronchitis in Britain, and its distribution within the country, are therefore a legacy of poor social conditions in the past. Particular adverse influences which are implicated include inadequate housing, large family size, overcrowding in the home, and the abandonment of breast feeding. This interpretation is consistent with the progressive changes, and sometimes encephalopathy, mimicking Reye's syndrome can be produced by viral infections in animals who have been exposed to a variety of exogenous agents. These include dicophane (DDT), fenitrothion (an organophosphate), butylated hydroxytoluene, pentenoic acid, and pesticide emulsifiers such as polyoxyethylene and Toximul Some of these effects are limited to particular genetic strains. A common theme in the animal work is the increased susceptibility of the young or fasted to mitochondrial dysfunction. It is not clear whether these agents act on peripheral tissue metabolism causing a catabolic state, influence the immune system, cause metabolic abnormalities which interfere with intermitochondrial protein synthesis and thus lead to a secondary disturbance of mitochondrial function or whether these environmental agents interfere with the interaction of the virus with mitochondria. These agents could interfere with metabolic processes leading to increased accumulation of toxic products in a fashion similar to that which is believed to occur in patients with isovalericacidaemia who are given aspirin. Aspirin inhibits glycine conjugation and may precipitate more severe encephalopathy.

With the present swing away from aspirin towards paracetamol in children, we should remember that in mice exposed to an emulsifier and mouse adapted influenza B virus, mortality was increased if the animals were given paracetamol or aspirin. Furthermore, encephalopathy with liver failure has been reported in a 15 month old infant who received four 500 mg tablets per day over a four day period before the onset of the liver failure.[3] He had received intermittent paracetamol for fever in the previous month.

As you assiduously complete your orange British Paediatric Surveillance forms, anxious lest the next analysis of returns will show that your unit has been responsible for the relatively low rate of return in your region, pause at Reye's syndrome. It is still with us and with many unresolved problems We have much to learn about the influence of environmental factors and genetic make up on our response to viral infection.

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Commentary

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The decision to severely restrict the use of aspirin in children in the United Kingdom was probably influenced by components of the carefully analysed study by Hall and her colleagues. Please note that 40% of the cases in the study were not thought to have taken aspirin before or during their illness. Note that four out of five of the cases who had taken aspirin had taken it in the past without ill effects. Note too that the authors conclude that 'If aspirin has an aetiological role there must be an exceptional unpredictable combination of circumstances that act as a trigger.' Reye's syndrome 25 years after it was first defined still presents many challenges.[1 2]

For the clinician the first is early consideration of the diagnosis in any child with encephalopathy and vomiting so that steps can be taken to prevent a further increase in intracranial pressure and so that glucose may be given intravenously in sufficient concentration to provide energy for cells deprived because of disordered mitochondrial function. The second challenge is to arrange appropriate investigations to identify genetically determined metabolic disorders which may present as Reye's syndrome. At least 23 have been reported to date. Defects of fatty acid oxidation and urea synthesis can cause particular difficulties in diagnosis While most of these disorders present before 3 years of age, presentation in the second and third decade has been reported.

Accurate diagnosis may only be possible if samples of serum or urine have been collected in the acute stage and stored at −70°C for subsequent analysis. It is not clear how many of these disorders have been rigorously excluded in any of the epidemiological studies. We should be very cautious about diagnosing cryptogenic Reye's syndrome in the first three years of life. Accurate diagnosis of alternative genetic disorders is essential for genetic counselling and to prevent relapse with the risk of brain damage or death in the proband Siblings may be at risk, not only of Reye's syndrome but of 'cot death'.

In cryptogenic Reye's syndrome there are two characteristic but *unexplained* pathogenic phenomena

(1) An unusual disturbance of mitochondrial structure associated with a decreased activity of all mitochondrial enzymes, best documented in liver tissue These abnormalities are most severe in the first 48 hours after onset, progressively returning to normal within five to nine days Other subcellular organelles show only minor changes

(2) An intense catabolic state, the duration of which seems to be similar to the mitochondrial abnormality

At least 19 different viruses, including examples from major groups of RNA and DNA containing viruses, have been implicated in the viral prodroma. Viruses are rarely recovered from the liver or brain. Just why such viral infection could cause a specific mitochondrial lesion in between 1:20 000 to 1:500 000 of children infected is quite unknown. In laboratory studies it has been shown that hepatic exposure, there still remained a significant case-comparison difference in the overall proportions given aspirin.

(5) OTHER ISSUES

Demonstration of a dose-response relation is one of the classic criteria of causality. Although a significant excess of cases exposed to aspirin had been given adult preparations, we made no formal attempt to study dose-response for several reasons: (a) indices of response, such as coma stage on admission or outcome that have been used in earlier studies,[4,15] are subject to many confounding variables linked to the wide range of treatments used; (b) aspirin pharmacokinetics in the Reye's syndrome prodrome may differ from those in normal children with a trivial febrile illness;[3,16,17] and (c) if the role of aspirin is idiosyncratic or adjuvant, dosage may be irrelevant

The finding that almost four fifths of cases given aspirin, had been so exposed in the past, without ill effects, shows the complexity of the aetiopathogenesis of Reye's syndrome If aspirin has an aetiological role there must be an exceptional unpredictable combination of circumstances that act as a trigger

Three of the studies in the United States gave data on the types of salicylate to which cases had been exposed.[2,7,9] Although some of those patients, as in this series, had been exposed to non-aspirin salicylates, only three patients out of all four studies had not also taken aspirin. Non-aspirin salicylate exposure in our study may have been incompletely ascertained, however, because some parents may not have perceived such preparations as medications. The possibility of a role for these agents in Reye's syndrome remains unknown.

Conclusions

We have emphasised the complexities of conducting an epidemiological risk factor study to assess the role of preadmission aspirin in Reye's syndrome. This was not a prospectively designed formal case-control study, and, as in the studies in the United States, some inherent biases were present whose influences were unmeasurable. Nevertheless our findings suggest that an association between Reye's syndrome and preadmission aspirin may exist, which together with the finding of a reverse association with paracetamol confirms published results.[4–8]

We are grateful to the many paediatricians and general practitioners who reported cases and who kindly gave permission to interview parents We thank consultant and nursing staff at St Georges Hospital, Tooting for permission and facilities to conduct interviews on paediatric and infectious disease wards Dr Glasgow wishes to thank Misses Susan Gray, Pauline Wilkinson, and Karen Clarke who ably helped with data collection We also thank Drs H Tillett, G Manning, and A Ades for computing and statistical advice Most of all, we thank the parents and the National Reye's Syndrome Foundation of the United Kingdom, without whom this study would not have been possible

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Appendix

'REYE SCORE'

(*a*) *Clearly defined prodrome*: yes=2; no=0; not recorded=1.

(*b*) *Vomiting*. moderate–severe=2; minimal=1; no=0; not recorded=1.

(*c*) *Serum alanine/aspartate transaminase*: raised three or more times normal concentration=3; raised less than three times normal concentration or concentration not specified=2; not raised=0; not measured/not recorded=1.

(*d*) *Plasma ammonia*: as (c).

(*e*) *Cerebrospinal fluid*: white cell count $\leq 8\times10^9/l$=2; white cell count $>8\times10^9/l$=0; not examined, or bloody tap, or not recorded=1.

(*f*) *Hepatic pathology*: macroscopically fatty but no histological examination=1; histological description. panlobular microvesicular fatty infiltration=3, histological description: 'typical or suggestive of Reye syndrome'=2; histology not recorded or not undertaken=0.

(*g*) *Investigations to exclude alternative diagnoses*: done=2; not done or not recorded=0.

(*h*) *One or more atypical features* (for example, family history, history of recurrent episodes, unusual presentation such as sudden death)=−2.

Highest possible score=17.

If patient initially met case definition but subsequently had the diagnosis revised (for example, as a result of histological findings at postmortem examination or of investigations for metabolic disorders) a score of 0 was allotted.

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straightforward matter to diagnose salicylate intoxication, certain inborn errors of metabolism which mimic Reye's syndrome have proved much more difficult to exclude with certainty.[12] Using the current standard case definitions, it seems likely that any series of 'Reye's syndrome' cases will contain some patients in whom, on more sophisticated investigation, specific metabolic disorders will be discovered. Unless it is postulated that aspirin has a role in such conditions it is not easy to explain the high proportion of cases given this medication in studies in the United States (93–100%). In contrast, only 59% of our cases were similarly exposed and it was this which made our novel method of analysis using the Reye score both valid and essential

Although clinical scoring is arbitrary and can easily be criticised, this exercise was carried out 'blind' to medication usage. The strong correlation between Reye score and aspirin medication in contrast with that with paracetamol was therefore both striking and surprising and may help balance a degree of diagnostic imprecision.

(c) Comparability of case and comparison patients

Although this was not conceived as a formal case-control study, if inferences are to be drawn from differences in antipyretic use the characteristics of the two groups should be compared. The comparison patients were slightly younger than the cases. Comparison of age specific aspirin exposure rates, however, still showed a significant excess among the cases of Reye's syndrome who were less than 5 years of age (as well as in those less than 12 months of age). In the older group the small numbers of comparison patients may have prevented detection of a true difference. We cannot therefore conclude that aspirin does not have a role in these older patients.

There were geographical differences in the use of aspirin, possibly reflecting different parental and professional attitudes to choice of antipyretic All of the cases in Northern Ireland and Scotland were so treated and the rates of aspirin ingestion were also significantly higher in Belfast than in London comparison patients. Geography alone, however, was not a major confounding variable, as there were still significant case-comparison differences in aspirin exposure within Northern Ireland and England when analysed separately

The variables that influence the choice of an antipyretic in an acute febrile childhood illness are largely unknown. American parents may be more likely to use aspirin than paracetamol for more severe illness as judged by the height of fever.[9] The effect of this variable was difficult to compare in our case and comparison groups because, although fever was reported by parents to be the most severe preadmission symptom in comparison patients' parents (in contrast with cases among whom it was vomiting), the majority in each group assessed its presence and degree by touch rather than by thermometer measurement. The very slight difference in prodrome duration might, if anything, have led to cases of Reye's syndrome receiving fewer antipyretics, but in fact the overall proportions receiving these drugs in each group were similar. Whether the qualitative differences between the two groups in the range of symptoms influenced the choice of antipyretic is speculative. Parents of cases tended to report symptoms that might have reflected rising intracranial pressure, while those of comparison patients described those suggestive of a viral upper respiratory infection (figure) Although family doctors were consulted significantly more often by the cases, there was no difference in the proportions of total medications given to each group that were antibiotics, which suggests a degree of comparability in severity.

(3) RECALL AND REPORTING BIAS

In contrast with the parents of children with Reye's syndrome, parents of comparison patients were interviewed within a few days of onset and this may have helped minimise recall bias associated with less severe illnesses compared with that of the cases. Whether the seriousness of the illness of the cases improved recall by their parents and balanced the influence of the longer admission to interview intervals is speculative. It did not appear to affect antipyretic reporting rates, brand name recall ability, or to result in significant disparity with BRSSS medication data.

The apparent association between 'prior knowledge' of aspirin as a risk factor and likelihood of reporting preadmission aspirin may reflect a serious reporting bias. This bias, whose detection and prevention would be extremely difficult, was not addressed in the studies in the United States where parents were likely to have been more informed because of both national and local publicity campaigns. In our study it is hard to see how reporting bias could have influenced the Reye score findings, which still showed a significant association with aspirin within the group with 'no prior knowledge'.

(4) PROTOPATHIC BIAS

It is arbitrary, and, if aspirin has an exacerbatory rather than an initiator aetiological role, possibly irrelevant, to identify the point of onset of Reye's syndrome After excluding cases in whom the day of onset (on our definition) coincided with aspirin

Discussion

The findings of this study suggest that there is an epidemiological association between the development of Reye's syndrome and use of aspirin during the viral prodrome. Significant differences were shown between the cases of Reye's syndrome and comparison patients as a whole, for those under 5 years of age, and for the English and Northern Ireland groups separately. Cases of Reye's syndrome were more likely than comparison patients to have been given two or more aspirin preparations. There was also a strong relation between diagnostic precision of Reye's syndrome, as measured by the Reye score, and the likelihood of prior aspirin medication.

When interpreting these findings, several important methodological issues must be addressed. These exemplify the inherent difficulties in an epidemiological study of medication risk factors in a condition such as Reye's syndrome.[13]

(1) DATA COLLECTION BIASES

(a) Emotional background to interview

All the parents of children with Reye's syndrome had lived through a major life event after which they had had varying lengths of time to adjust. For many this interview was their first opportunity to ventilate concerns and anger about possible causes and avoidability. In contrast with the studies in the United States, which were mainly conducted while the index case was still in hospital[4-8] (and which make no reference to parental emotional state) our case interviews were carried out in the home and when outcome was known. Our comparison parents, interviewed in hospital, may have been in a somewhat more stressful setting, although none of these patients required intensive care. The effect of these differences on comparability of recall accuracy between the two groups is difficult to assess

(b) Interviewer bias

Limited resources meant that the same person was concerned both with the preparation for, and the conduct of, the risk factor study. The principal interviewer was, therefore, fully aware of published aetiological hypotheses about Reye's syndrome On the other hand, because of striking epidemiological differences in Reye's syndrome between the British Isles and the United States,[11] there seemed no cogent reason why the same risk factors might apply. From the outset our approach was, therefore, to study a wide range of risks, rather than concentrate on the narrower field of prodromal medication.

As in the studies in the United States, it was impossible for the principal interviewer to be unaware of the group (case/comparison) to which parents belonged, and difficult to see, given the serious nature of Reye's syndrome (47% of the cases we studied died) how this bias could have been avoided.

(c) Product identification

In contrast with the studies in the United States, this was more possible in the children with Reye's syndrome whose parents were interviewed at home than in the comparison groups seen in hospital. Although direct sighting always confirmed parents' statements, the numbers concerned were small. The value of this method of verification is questionable, however, as it takes no account of other unrevealed drugs in the home.

(2) SELECTION BIAS

(a) Excluded cases

There were minor demographic and clinical differences between these and the included cases, but it is not felt that their omission introduced any systematic bias. We attempted to measure antipyretic exposure in these patients from BRSSS data. Although the proportions reported as receiving aspirin were lower in the two groups of excluded cases than in the group interviewed, the value of these data was hampered by small numbers and the non-standardised manner of collection

It could be suggested that some clinicians might only make a diagnosis of Reye's syndrome whenever a patient had actually received aspirin. This issue was a major criticism[10] of the pilot study in the United States, which took place during a time of heightened public debate concerning the role of aspirin.[7] Although there had been some publicity in the United Kingdom before this study, there was little media attention until the Committee on Safety of Medicines announcement in June 1986. Furthermore, the only clinical series published in the United Kingdom at the time of the study had found no evidence to support the then strongly disputed Reye's syndrome-aspirin association.[14] Thus although there could have been some selection bias because of an unrepresentative case sample, this seems unlikely in the study period concerned.

(b) Subject classification

The epidemiological case definition of Reye's syndrome is sensitive but non-specific A precise diagnosis remains problematical, depending upon an amalgam of clinical and biochemical features, supported by histopathological and ultrastructural data. Not all of our cases, however, conformed to this exacting standard. Similar criticisms may be levelled at the case-control studies from the United States that used broadly similar criteria While it is a the Republic of Ireland, and two of the four in Wales had been given aspirin

REYE SCORE

There was a strong association between this score and the likelihood of receiving an antipyretic (table 4). Analysis by type of medication showed a highly significant correlation between aspirin exposure and Reye score (trend p=0·00001), in contrast with that with paracetamol (p=0·07) Eleven out of the 12 cases with scores of 15–16 had had aspirin, compared with none of the four with scores of 0–4. Further analysis suggested that this link between the Reye score and aspirin use was age independent.

In the following analyses we attempted to estimate the presence and effect of certain biases (for example, recall, prior knowledge, protopathic bias, and different case-comparison illness dates) which might have influenced case-comparison differences in antipyretic exposure. In the cases with Reye's syndrome there was no relation between admission to interview interval and the use of aspirin, paracetamol, or neither antipyretic. Parents could recall the aspirin brand name in a similar proportion of case (59/68, 87%) and comparison patient (44/48, 92%) aspirin exposures. Among these a higher proportion of cases had received an adult preparation (37/59, 63%) compared with comparison patients (11/44, 25%) (p=0·00002).

Reported preadmission aspirin usage among the 57 (54%) parents of cases who volunteered prior knowledge of a Reye's syndrome–aspirin association was compared with that among the 49 parents who did not volunteer such knowledge. The proportions were 45 (79%) and 18 (37%), respectively (p=0·0002). An analysis of Reye score and antipyretic exposure within the 'no prior knowledge' group, however, still showed a highly significant correlation between this score and aspirin (but not paracetamol) exposure.

Parents' reports of aspirin use were compared with the original reports to BRSSS from the notifying clinician. Because of an alteration in the surveillance questionnaire, comparable data were available for only 33 cases. There was agreement in 28 (85%) Of the remaining five, the BRSSS indicated that four had not been given aspirin, whereas the risk factor study response was that it had; the reverse was the case in one other.

BRSSS data were also used to compare aspirin use in the cases whose parents were excluded from interview, with that in cases whose parents were interviewed. Limited data on antipyretic use were available for 65 excluded cases and suggested that four out of 17 (24%) of those approached and 25 out of 48 (52%) of those not approached had received aspirin. This compared with 63 out of 106 (59%) in those interviewed.

An attempt was made to exclude protopathic bias by repeating the case-comparison analysis of aspirin exposure after exclusion of cases of Reye's syndrome given aspirin on the day of 'onset' or thereafter. 'Onset' was arbitrarily defined as the first day on which anorexia, vomiting, drowsiness, or behavioural change occurred, except where the latter was reported within 24 hours of prodrome onset. Thus defined 17 cases were excluded: 10 out of 33 who were less than 5 years of age and seven out of 30 who were 5 or older. A significant difference remained between the two groups as a whole (p=0·004), although this disappeared in cases less than 5 years of age taken separately (p=0·38)

There was no significant difference between aspirin exposure rates among Belfast comparison patients interviewed in 1986 and those interviewed in 1985. Exclusion of the former from case-comparison analyses did not reduce the levels of significance of the differences in aspirin exposure.

If the analysis was restricted to those cases and comparisons with onsets in 1985, the difference in aspirin exposure (10/12 (83%) compared with 32/133 (24%) respectively) was even more striking than among the two groups as a whole.

Table 4 *Reye score in relation to antipyretic exposure*

*Score**	*No of patients*	*Aspirin No (%)†*	*Paracetamol No (%)‡*	*No antipyretic No (%)§*	*Total No (%)*
0–8	22	5 (21)	7 (29)	12 (50)	24 (100)
9–10	29	13 (38)	11 (32)	10 (29)	34 (100)
11–13	30	23 (68)	5 (15)	6 (18)	34 (100)
14–16	25	22 (79)	4 (14)	2 (7)	28 (100)
Total	106	63	27	30	120

*Groups divided into (approximate) quartiles for statistical efficiency
Trend p values †0·00001, ‡0·07, §0·003.
Row totals do not add up as some subjects had each antipyretic

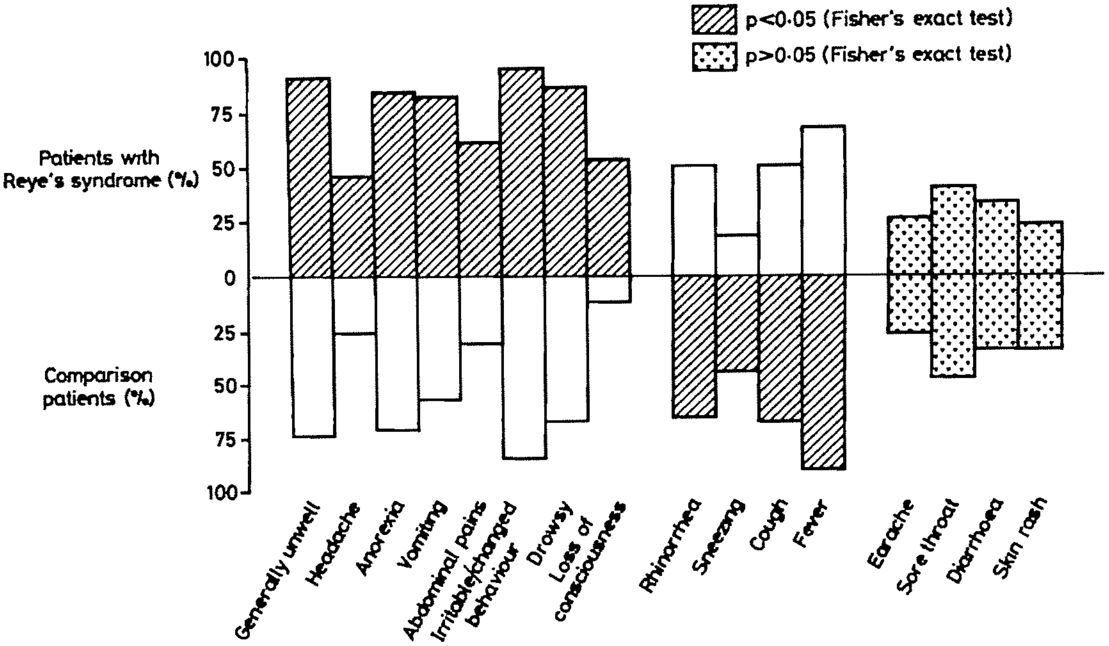

Figure *Preadmission symptoms in cases of Reye's syndrome and in comparison patients expressed, for each symptom, as proportion of total subjects for whom information available (49–100% cases and 37–100% comparisons, depending on symptom)*

also had aspirin had been given non-aspirin salicylate, compared with nine comparison patients, five of whom had had aspirin; the most frequent preparation was a teething gel containing choline salicylate.

Analysis of antipyretic exposure by age (those less than 5 years compared with those 5 or more) showed that an excess of the cases of Reye's syndrome had been given aspirin in each group, although in the older cases this difference just failed to reach significance (table 3). Conversely, among comparison patients in both age groups there was excess exposure to paracetamol but in the younger group significance was not achieved.

Among London comparison patients, there was no difference in aspirin use when comparing white children with other ethnic groups as a whole.

An analysis of aspirin use in England and Northern Ireland separately was undertaken. In Northern Ireland all 14 children with Reye's syndrome had received aspirin compared with 32 (38%) of the comparison patients (p=0·00002). In England, by contrast, 38 (49%) of the 78 cases had had aspirin compared with 16 (16%) London comparison patients (p=0·000004). Belfast comparison patients had received aspirin significantly more frequently than those in London (p=0·0014). All six cases of Reye's syndrome in Scotland, three of the four in

Table 3 *Antipyretic exposure in relation to age in Reye's syndrome cases and comparison patients*

Antipyretic	*Aged <5 years*		*p Value*	*Aged 5 years and over*		*p Value*
	Cases No (%)	*Comparisons No (%)*		*Cases No (%)*	*Comparisons No (%)*	
Aspirin	33 (49)*	41 (24)*	0·0005	30 (79)	7 (50)	0 07
Paracetamol	24 (35)	84 (49)	0 07	3 (8)	7 (50)	0·004
Total in age group	68	171		38	14	

*Includes 18/39 cases *v* 13/85 comparison patients who were <1 year old, p=0·0008

Table 1 *Characteristics of 264 cases of Reye's syndrome reported to the British Reye's syndrome surveillance scheme*

	Included in risk factor study	*Omitted from risk factor study*	
		Approached	*Not approached*
No of children	106	44	114
Median age (months)	23	14	11
Year of onset (%):			
1981	7	5	19
1982	14	31	32
1983	34	38	19
1984	34	18	31
1985	11	8	0
Country (%)			
England	74	75	57
Northern Ireland	13	6	22
Scotland	6	6	7
Wales	4	9	3
Republic of Ireland	4	3	11
Mortality (%)	47	64	48

Those interviewed were slightly older and had a more recent onset than those excluded (table 1). Mortality was higher in those not included after the initial approach and there were more cases not approached in Ireland.

COMPARISON PATIENTS

Of the comparison patients 100 were interviewed in London and 85 in Belfast; the median admission to interview interval was two days (range 24 hours–13 days). One hundred and thirty three interviews took place in 1985, April to December, and 52 (all Belfast) in 1986, January to mid April.

COMPARABILITY OF CASES AND COMPARISON PATIENTS

Cases of Reye's syndrome were older (table 2), but social class distribution was similar. There were significantly more white children among the cases (97% compared with 84%, p=0·0006). The figure shows preadmission symptomatology: cases were significantly more likely to report headache, anorexia, vomiting, abdominal pain, drowsiness, altered behaviour, and unconsciousness, while more comparison patients had fever, rhinorrhoea, cough, and sneezing

Table 2 *Age distribution of Reye's syndrome cases and comparison patients*

*Age**	*Cases*	*Comparison patients*		
		London	*Belfast*	*Total*
	No (%)	*No (%)*	*No (%)*	*No (%)*
12 months	39 (37)	45 (45)	43 (51)	88 (48)
13–60 months	29 (27)	43 (43)	40 (47)	83 (45)
5–10 years	23 (22)	10 (10)	2 (2)	12 (7)
11–15 years	15 (14)	2 (2)	—	2 (1)
Total	106	100	85	185

*Median age of cases was 23 months median age of comparison patients was 13 months

Mean (SD) length of preadmission illness was 8·4 (8·6) days in the cases of Reye's syndrome and 10·4 (10·7) days in comparison patients. The family doctor, consulted for 92% of cases and 81% of comparison patients (p=0·01), prescribed one or more drugs for 84% and 81% of these, respectively. In the three weeks before admission, the mean number of drugs (prescribed and over the counter) received by the two groups was 2·2 and 1·9 per patient. Forty four (19%) of 230 drugs given to the cases were available for inspection, in contrast with four out of 344 (1%) given to comparison patients (all confirmed parents' statements). Antibiotics accounted for 47 (20%) and 86 (25%) of all drugs given to the cases and comparison patients, respectively (p=0·24).

EXPOSURE TO ASPIRIN AND PARACETAMOL

Although similar overall proportions (72% compared with 68%, p=0·64) of cases and comparisons had received antipyretics, 63 (59%) cases and 48 (26%) comparison patients had had aspirin ($p<0·0000001$), five cases but none of the comparison group had been given two proprietary forms. Twenty seven (25%) cases had been given paracetamol compared with 91 (49%) comparison patients (p=0·00015). Fourteen (13%) cases and 16 (9%) comparisons had received both antipyretics. Fifty (79%) of the cases given aspirin had had this medication with no ill effects in the past.

Six cases of Reye's syndrome each of whom had

Patients and methods

(1) ASCERTAINMENT OF CASES OF REYE'S SYNDROME AND COMPARISON PATIENTS

Cases of Reye's syndrome were ascertained by the BRSSS from voluntary reporting by paediatricians, other health professionals, parents, and from copies of death drafts supplied by the Office of Population Censuses and Surveys and the General Registry Office for Scotland. Parental permission for an interview was sought after agreement of their paediatricians and family doctors Comparison groups consisted of children admitted with acute febrile illnesses to two teaching hospitals—one each in South London and Belfast.

(2) DATA COLLECTION

Cases of Reye's syndrome and London comparison patients were interviewed by the same person; two senior medical students conducted the Belfast comparison interviews These took place in the homes of the cases of Reye's syndrome; parents of comparison patients were seen on the wards. A prepiloted, semistructured questionnaire was used to seek information from the parents of cases of Reye's syndrome on social background, the child's and the family's medical history; symptoms, severity, and duration of the prodromal illness. Questions were also asked on risk factor exposure: (a) details of all medications given in the three weeks before admission—for example, names (visual verification was also requested), dates, dosages, and whether ever given before; (b) contact illness history; (c) travel history; (d) environmental exposures—for example, chemicals, insecticides, sick animals, and (e) diet. Finally, parents were asked about prior knowledge of specific risk factors.

The comparison patients' questionnaire was identical to that used for the cases of Reye's syndrome but omitted questions relating to risk factors other than medications.

(3) DIAGNOSTIC CRITERIA

Cases of Reye's syndrome conformed to the BRSSS definition.[11] As even with 'typical' histology this definition is relatively non-specific and distinction must be made from other encephalopathies,[12] each case was also allotted a score (see appendix). This was based on all the clinicopathological features of Reye's syndrome and was an arbitrary measure of how closely the patient fulfilled the diagnostic criteria. Scores ranged from zero to 17—low scores reflecting those in whom the diagnosis was not confirmed and maximum scores reflecting patients who were characteristic in all aspects. Scoring was done without knowledge of risk factor exposure.

Comparison patients consisted of previously healthy children with an acute febrile respiratory, intestinal, or other (infectious) illness who did not develop Reye's syndrome. Any selection was entirely dependent upon interviewer availability

(4) DATA ANALYSIS

Completed questionnaires were coded, entered on computer, and checked for coding errors using a quality assurance sample. Statistical analysis was performed using the 'Minitab' package and probability values calculated using Fisher's exact test (two tailed).

(5) ETHICAL APPROVAL

This was obtained from the ethical committee of the Public Health Laboratory Service and from the appropriate ethical committees for the comparison group studied.

Results

CASES OF REYE'S SYNDROME

Altogether 264 cases were reported to the BRSSS between 1 August 1981 and 31 July 1985 when recruitment to the risk factor study terminated. The parents of 106 patients were interviewed between April 1984 and October 1985. The median admission to interview interval was 10 months (range, 11 days–5·7 years).

Fifty one of the interviewed cases had had histological examinations all of which showed changes characteristic of Reye's syndrome. Of 56 survivors, 10 had sustained severe and two minor, neurological damage. There were two patients with juvenile chronic arthritis (an unexpectedly high prevalence) who were being treated with long term aspirin at onset of Reye's syndrome

The physicians of 44 others were approached but these cases were not included for the following reasons: because of the parents' emotional state permission to interview was refused by the medical attendants of 13, and in one case the parents themselves refused; 26 were impossible to contact; in two the diagnosis was revised after the initial approach, and in two others the study ended before the interview could be arranged.

In the remaining 114 cases the medical attendants were not approached for various, mainly administrative reasons—for example, the family doctor's name or parental address were unavailable (n=43); the report was received after data collection had ceased (n=17); the geographic location was incompatible with the approaching end of the study (n=13), diagnostic revision was already established (n=22), and diagnostic uncertainty (n=19).

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Controversy

Preadmission antipyretics in Reye's syndrome

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SUMMARY The parents of 106 children who had had Reye's syndrome and those of 185 comparison children who had febrile illnesses were interviewed in order to compare preadmission medication exposure rates in the two groups. Although comparable proportions of case and comparison patients had taken antipyretics in the three weeks before admission, a significant excess of cases (59% compared with 26% in the comparisons) had been given aspirin, whereas significantly more comparison children (49% compared with 25% in the cases) had taken paracetamol. There was an excess exposure to aspirin in children under 5 years of age; the excess observed in older patients just failed to reach significance. Separate analyses within Northern Ireland and England also showed a case-comparison difference. A significant correlation was shown between aspirin (but not paracetamol) exposure and the closeness with which cases conformed to the diagnostic criteria of Reye's syndrome, measured by an artibrary score.

The many difficulties of conducting and interpreting the findings of an epidemiological risk factor study of an association between aspirin and Reye's syndrome are reviewed and emphasised. Inherent biases were present in this as in previous studies and it did not conform to the classical case-control design Nevertheless the findings suggested that an association between Reye's syndrome and preadmission aspirin may exist in some children.

Reye's syndrome is a rare, serious childhood encephalopathy preceded by a viral prodrome and associated with curiously selective hepatic dysfunction.[1] Although its aetiology and pathophysiology are poorly understood, causation is believed to be multifactorial.[2] Various toxic agents have been implicated, including aflatoxins, insecticides, and their emulsifiers. An association with aspirin, first mooted 25 years ago,[3] was a consistent finding in five case-control studies conducted in the United States from 1978–86.[4–8] Although these studies have been critised,[9, 10] the strength and consistency of the evidence was such that in 1985, the United States public health authorities required warning labelling on aspirin-containing products and initiated a public education campaign against use of aspirin in children with feverish illnesses

The British Reye's Syndrome Surveillance Scheme (BRSSS), which began in August 1981, is an ongoing joint venture of the British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre.[11] Its principal aims are to document the epidemiology of Reye's syndrome in the British Isles and to provide a case registry for future more detailed studies

This report, based on cases notified to the BRSSS, presents some of the findings of a two year risk factor study. The aim was to collect detailed preadmission data in cases of Reye's syndrome in order to generate aetiological hypothesis that might then be tested in controlled studies. Initially the study was designed to gather information on a wide range of possible risks rather than to focus on any single hypothesis. After publication of the fourth (pilot) study from the United States[7] and preliminary analysis of our data, however, it was decided to recruit two comparison groups of patients in order to clarify findings in relation to preadmission medication

Unfortunately in the past, and sadly still in the present, bereaved parents are not helped as much as they could be by professionals who block the reality of the experience by misplaced kindness because they try to spare parents the pain of seeing and holding, for example, a malformed baby. We have now learnt, however, how to clothe such a baby to make it easier for the parents. The routine photography of all stillborns, and now even miscarriages,[10 11] and practices such as giving parents the baby's name tag, lock of hair, or other momento shows how much progress has been made. While an experienced and interested midwife, paediatrician, obstetrician, or social worker can provide help, everyone who is in contact with the family needs to be aware of the loss and the need that bereaved parents have of empathy for their state of mind and feelings.

Right from the start, with the first suspicion that there may be something amiss, a recognised and identified professional should be immediately available and it should be someone who hopefully will be available subsequently. From a practical point of view each team should try to evolve a first, second, and third person to be 'on call' for such help. The skills required are an interest in such needs and the ability to share with parents their grief. We are not all made for this work, but much of it can be taught and learnt, and if for personal reasons and one's own life events, we are not comfortable or suited to undertake this onerous task, we should be honest and say so, otherwise it is neither fair to parents or to ourselves.

The acute intensity of the moment of realisation calls for special skills, as when an infant is unexpectedly stillborn, when the ultrasound shows an abnormal fetus, or the amniocentesis shows abnormal chromosomes. We should recognise the subjective anxiety and fear that such situations can engender in junior nursing or medical staff and a protocol established for help from a named and identified senior member of staff.

In practical terms every member of the hospital staff should know that a bereavement counselling service is available, where it is held, and how appointments are made. It has always been my practice to arrange for the parents to see the consultant obstetrician who was in charge of them in the first instance and to see them myself soon after they have seen him whenever possible. The fact that both parents are invited together recognises how much they are both involved; so often I find fathers are left out. I find that a minimum of 45 minutes is almost always needed: at this initial interview time is necessary for the weeping and comforting that take place. A lot of the time may be spent in silence, as an acceptance of the poignancy of their feelings which makes talking difficult. I learnt by experience, after many mistakes, when to try to break the silence with an open ended remark such as 'many parents have ideas about why their baby died, which they think might sound foolish—a parent once asked me if it could have anything to do with the dog next door having been ill?' I find it easier at such interviews when I sit alongside them and not behind a desk. I was puzzled how best to make notes. I even tried taping the interview, but the secretarial time in transcribing such tapes proved prohibitive, as did the editing of them. Eventually I found that jotting down the main features of the interview immediately after they had left proved best and most useful when discussing this at the perinatal meeting and in the confidential letters to their general practitioner and the appropriate local health authority (with the parent's permission).

When bereaved parents talk things over with a counsellor—who may be any member of the hospital staff, chaplain, psychiatric social worker, or midwife as well as the obstetrician or paediatrician—it may not be easy for them as they will be burdened with painful emotions. What they choose to talk about is obviously what they are thinking about and what matters to them. Over the years I developed an operative check list of items I found of importance to them in their day to day living as well as in the future, and I bring up these subjects when the parents appear to have finished their choice of conversation. These items include for example: what siblings think and feel and how best to include them in the experience as their needs are unfortunately too often overlooked or underestimated and they can suffer in their bewilderment immediately and, most importantly, for a long time afterwards. There is also the ubiquitous embarrassment and discomfort that parents, relatives, friends, neighbours, and shopkeepers often experience, the impact of anniversaries; information about local support groups; and the time needed for adequate mourning before the next pregnancy and, above all, access for further counselling The skill required for such counselling is not easily acquired and the lessons learnt from mistakes prove invaluable for the future, albeit very uncomfortable at the time. It requires more than just the ability to listen, for one has to learn to hear what is being said and not being said, and what may possibly lay behind what they are saying and asking. More comes up for discussion than just the event and the quality of the marriage, and the parent's relationship has a considerable bearing on the support they can give and receive from each other.

The reason for the baby's death and the information parents require is important, but in practice not as much as I thought when I started. At first I thought that this would be a priority and I arranged for the first appointment to be six weeks after the baby's death in order to have the report of the postmortem examination to hand. Wigglesworth has pointed out succinctly how opportunities for pathological examination are still missed in the present day and what needs to be done to improve the situation.[11]

To see, to hold, and to name the baby, and to discuss funeral arrangements have become part of everyday practice in an ever increasing number of maternity units.

There is a natural inclination on everybody's part to try to wipe out the past and its pain and advise the parents to try for another baby as quickly as possible. Understandable as this reaction is, we have now learnt that such a 'replacement' does not achieve the desired aim. Without a period of adequate mourning, which should be at least six to nine months, the mother's unresolved grief can resurge and with even greater force when the new baby is born. It is not easy to know when the mourning process is sufficiently over to embark on the next pregnancy as the apparent recovery may, in fact be a state of denial. Pregnancy prevents adequate mourning and apart from the mother's resurgent grief the effect on the new baby of being a replacement can seriously affect the child's gender and identity.[12] There are those who fail to respond to the help we offer them. Despite frequent counselling sessions they may not show progress and this 'pathological grief' may need more expert help, perhaps from a psychiatrist with a special interest in perinatal death.

Like so much in this new field further study and enquiry are needed. Past life events may render parents more susceptible and vulnerable than others to a perinatal bereavement. The identification of these events, which may include perinatal bereav ments in previous generations, could alert us to b more prepared to pay special attention to suc families rather than be taken by surprise at th otherwise inexplicable 'over reaction' to this loss

What has happened up to date is most heartenin and encouraging. The help parents and families are now receiving is very worthwhile on humanitarian grounds and by its mental health preventive influence. The benefits of research in this challenging field will add greatly to the wellbeing of such families in the future.

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Correspondence

Hospital paediatric staffing

Sir,

Dr Nelson's call to the British Paediatric Association (BPA) to fight for improved medical staffing levels in district hospitals is most welcome.[1] I share his disappointment with the BPA's response[2] to 'Achieving a Balance'[3] which fails to acknowledge the fact that the present situation in many district hospitals is totally unsatisfactory. I would like to describe two issues concerning staffing levels that concern me.

Firstly, the position regarding numbers of senior house officers. We are more fortunate in this district than Gateshead. In cooperation with local community child health services we have secured adequate intermediate cover by the establishment of two 'experienced' senior house officer posts in addition to retaining, thus far, one registrar post. By so doing we have been successful in meeting the increasing demands on the service including that of providing intensive care for 4000 annual deliveries. These posts provide a comprehensive training—including community paediatrics appropriate for future consultant hospital and community paediatricians—for doctors with one or more years previous paediatric experience. Unfortunately I suspect that many 'teaching' hospital consultants do not acknowledge the value (or indeed the existence!) of these posts and therefore would discourage their senior house officers from applying for them.

As a result suitable candidates are difficult to attract. In the same issue of the *Archives* Drs McDowell and Gregg, writing as members of the Medical Womens Federation, stress the importance of district hospital experience in paediatric training.[4] Such experience is available in many hospitals at 'experienced' senior house officer level.

In the past seven years, of a total of eight 'experienced' senior house officers who have worked in this unit two are now consultants in their country of origin (Greece and Syria), and two are well on their way to becoming so having moved on to teaching hospital registrar posts. Two others (of more recent 'vintage') are registrars with MRCP part I in teaching hospitals. One has become a general practitioner with hospital sessions as a hospital practitioner in paediatrics and one has changed to anaesthetics with the intention of specialisation in paediatric anaesthesia and intensive care. These posts have therefore neither contributed to the 'bottleneck' in the hospital career ladder nor turned out to be 'dead end jobs'. Dr Jackson informs us that the BPA is currently conducting 'a comprehensive survey of paediatric manpower' but I suspect this does not include the senior house officer grade and in particular the 'experienced' senior house officer grade. The need for, and value of, these posts should be acknowledged (in the presence of a continuing 'freeze' on registrar posts) and their job content evaluated to ensure that they meet training requirements. Some posts could be converted to 'overseas doctor' registrar posts, although I cannot share the BPA's apparent belief that there is an ample supply of candidates.

Secondly, the other aspect that concerns me is the duration of training, which I believe is a deterrent to embarking on a career in hospital paediatrics. I see evidence of a dwindling in numbers at this time. One factor contributing to the problem is the apparent requirement for those in training to 'get an MD' before being considered for a senior registrar post. Not only does this lengthen the training period by two or three years, in most cases it is inappropriate and barely relevant except for a minority who see their future in academic medicine and research. More appropriate clinical research opportunities should be provided concurrently with normal registrar and senior registrar training. This requirement for an MD seems to have developed insidiously without debate, and should be reversed, if we are to continue to attract suitable young doctors into our specialty.

I think I speak for many district hospital consultants in expressing my fears for the future of our services and hope that our Association will respond vigorously.

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Dr Appleyard (convenor of BPA Manpower Committee) comments

As Dr Nelson has written,[1] 'Achieving a Balance'[2] has provoked the British Paediatric Association (BPA) to pronounce on the paediatric staffing needs in each health district, both in hospital and in the community.[3] Bearing in the mind the good points raised by Dr Evans-Jones, we did insist on the inclusion of paediatrics among those specialties who required a 'safety net'. This has exposed the current total inadequate provision of 'intermediate' paediatric resident staff, of which I am only too aware as a district general hospital paediatrician running an acute service without any registrar support. Shortly, district working parties are likely to be set up to review the 'safety net' as well as junior hospital doctors' hours. It is *vital* that all paediatricians put forward their own proposals for intermediate cover in their own health district and insist on this provision by the health authority in line with the national agreement. Dr Evans-Jones suggests that senior senior house officers could be one of the 'options' for this intermediate level care, together with visiting registrars, career registrars, and senior registrars Career and visiting registrar posts will in future have to be part of the same recognised rotation Visiting registrar posts will be open exclusively to foreign medical graduates, who will be able to stay in this country for the duration of their training only (up to five years on limited registration) There are currently some 115 foreign medical graduates occupying the 287 paediatric registrar posts. It is likely that there will be a minimum of 100 posts available for visiting registrars There is *no* manpower limitation, however, on the numbers of visiting registrars envisaged in 'Achieving a Balance' The initiative taken by the BPA must be matched by local action from paediatricians in the regions to construct appropriate training programmes for the present and any future visiting registrar appointments

Anticipating the likely consequences of 'Achieving a Balance', and the increased authority of the Joint Planning Advisory Committee (JPAC), the BPA Manpower Committee, after careful consultation and 'piloting', carried out a nationwide comprehensive survey of paediatric manpower in 1986 The results—available to all members—have been collated and used in our submission to the JPAC. Professor Forfar, the President of the BPA, and I gave oral evidence on behalf of the Royal College of Physicians. We found that the Department of Health and Social Security (DHSS) figures seriously under-recorded the number of consultant paediatric career opportunities in England and Wales (the BPA survey in 1986 recorded 744 consultants, the DHSS 629 consultants) This discrepancy is mainly due to the DHSS failure to record the 'paediatric' specialists. The first request of the DHSS to the regional health authorities regarding future new consultant paediatric posts did not include a significant number in community child health The DHSS officers have therefore been shortchanging our specialty in their calculations for the need for future training posts In the next six months they will be consulting Regions as to whether they would, if offered, be able to create extra senior registrar posts in community child health It is important, therefore, that this initiative is seized by paediatricians in all the Regions

The JPAC have had their terms of reference extended to include paediatric registrars. These 'figures' will be the subject of their scrutiny next year. The Council of the BPA has wisely already decided to initiate a further detailed study of paediatric manpower requirements in each health district to provide us with the weapons to fight for our specialty's needs. We eventually achieved a one hundred per cent response from our 1986 survey and we are looking for the same commitment from paediatricians again this year

For the BPA to be successful it is essential that all paediatricians are involved in the manpower planning process and keep up to date with the fast moving events, not only through our BPA Newsletter, but with their regional representative on the BPA Council regional advisers in paediatrics, and chairmen of their regional paediatric advisory committee and any training subcommittee, so that a coordinated paediatric response can be made in each region.

In the December Newsletter I suggested the following checklist

(1) See whether your health district is going to convert senior clinical medical officer posts into consultant paediatricians (community child health) posts over the next few years

(2) Make sure these are included in your district plan so that the numbers can be counted centrally by the regions

(3) Insist on a proper 'safety net' in order to run the acute paediatric service in your health district.

(4) Urgently activate your regional paediatric committees in association with university teaching hospitals to institute competitive schemes for 'visiting' registrars.

'Achieving a Balance' is an important document. It could enable a significant improvement in paediatric manpower to occur providing each one of us in paediatrics takes the initiative On the other hand, if we fail to get to grips with the detail and do not become involved locally in our own districts, our specialty could suffer significantly in the new planning process.

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Precocious and premature puberty associated with treatment of acute lymphoblastic leukaemia

Sir,

We have read with great interest the article by Dr Leiper and coworkers regarding pubertal development and growth after treatment for acute lymphoblastic leukaemia [1] Their results agree, on several important points, with our earlier findings on disturbed pubertal growth in girls after acute lymphoblastic leukaemia [2]

There are, however, some methodological differences in the two studies which make direct comparison difficult. All the girls in our study were followed until menarche, and are in this respect comparable with the group of 55 girls in Dr Leiper's study, used for relating the age of onset of treatment to age at menarche (his ref 1, fig 3)

Menarche is the single point in the pubertal development which is easy to date precisely, and as such perhaps the most suitable for comparisons of puberty. It would be interesting to know the mean age for menarche in Dr Leiper's subjects Girls who showed pubertal development in close connection to the diagnosis should of course be excluded.

The significantly lowered mean age at menarche in our subjects was not due to precocious puberty in a few cases but rather to early-normal puberty in the majority of girls.[2] One wonders why Dr Leiper did not analyse in more detail the growth and development of the well defined group of girls who attained menarche and instead formed a selected group with evidence of early pubertal maturation.

Interestingly enough, the growth pattern of the girls followed to final height who were reported in Dr Leiper's article, agrees very well with the results presented by us.[2] Dr Leiper and coworkers do not analyse the growth data of the 55 girls who attained menarche. In our study the average height decreased from −0·5 SD before puberty to a mean final height of −1·5 SD. This loss in stature was due to a subnormal growth spurt.

Analysis of spontaneous growth hormone secretion during 24 hours indicates that girls treated for acute lymphoblastic leukaemia, including cerebral irradiation, have severely blunted growth hormone secretion already before puberty (C Moell *et al*, unpublished data). Growth at that time, however, is normal.

The growth hormone insufficiency of these girls seems to be relative and manifests itself only when the increased demands for growth hormone during puberty cannot be complied with. In patients who lack an adequate growth spurt the onset of early puberty will cause additional impairment of final height. In this respect we agree with Dr Leiper that precocious and premature puberty can be an important factor in contributing to short stature in girls treated for acute lymphoblastic leukaemia.

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Drs Stanhope, Leiper, and Chessells comment.

Unfortunately, the paper by Dr Moell and coworkers was received after our manuscript had been submitted. We agree with most of their findings but we wish to indicate several important differences.

Four of the 10 patients described in Dr Moell's paper had received craniospinal irradiation and it is not appropriate to include these children in the analysis of peak height velocity without data on sitting height and subischial leg length growth velocities. Moreover, the fields for spinal irradiation in early childhood may well have included ovarian tissue. No data were given for the onset of puberty in the patients described by Dr Moell's group. The fact that the patients were all girls is interesting, however, and supports our hypothesis for the difference in timing of the onset of puberty in normal girls and boys.[1] We excluded patients who had developed early puberty soon after receiving cranial irradiation, as stated in our paper, mean age at treatment was 4·0 years (range, 1·4–7·8) whereas mean age for the onset of puberty was 8·8 years in the girls and 9·3 years in the boys.

Although menarche is an easy event to date precisely, it has little physiological meaning. Menarche does not usually indicate the onset of fertility and the mechanism of a uterine 'withdrawal bleed' is simple compared with the intricate endocrine events preceding an ovulatory cycle. We only used menarche retrospectively to correlate the timing of cranial irradiation and sexual maturation.

We agree with many of Dr Moell's comments about the growth of children with acute lymphoblastic leukaemia treated with prophylactic cranial irradiation; the predominant loss in height of such children is during the pubertal growth spurt. Although sex steroids are synergistic with growth hormone, the onset of the pubertal growth spurt is contemporaneous to a large increase in growth hormone pulsatility and indeed growth during puberty correlates with growth hormone secretion.[2] It is not surprising that the predominant impairment in the growth of children who have growth hormone insufficiency secondary to cranial irradiation is during the pubertal growth spurt.[3]

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Increasing medical burden of child abuse

Sir,

I share Drs Sharma and Sunderland's concern about the increasing medical burden of child abuse.[1] In Central Birmingham Health District, with 43 000 children aged up to 15 years, health visitors now attend over 300 child abuse case conferences annually. We too are experiencing an appreciable increase in referrals which subsequently prove to be unfounded. School and nursery staff have heightened awareness, but this has increased the rate of false positive referrals. It is well recognised that identified child abuse is more common in children from socially deprived backgrounds. Such children are also more likely to sustain accidental injuries. My concern is that an unexplained bruise found on the inner city child of inarticulate parents, socially distanced from professional staff, may be much more likely to result in a child abuse investigation than an identical bruise in the advantaged child of middle class parents.

The circumstances which lead families to abuse their children are complex, and not confined to particular classes of society. I cannot agree with Sharma and

Sunderland's concluding paragraphs, which have political overtones and are largely unsupported by evidence. I find it offensive to read of 'a subclass that can only better itself by sinking further.' There is abundant evidence that parents, even in the most difficult circumstances, have high standards for their children and strive to achieve these.[2] The concept of the cycle of deprivation has been vigorously challenged by those who stress that it is the structures of society, rather than individuals, which are most to blame for deprivation.[3]

Biological factors may be important but I cannot see the relevance of lactating hamsters. Other mammals defend their young with vigour I had considered satisfactory housing a basic human right What 'misuse' of housing could justify restriction of parental rights? Thanks to AIDS, access to contraception is freer than it has ever been but this is unlikely to affect the fertility rate of biologically immature young people. On a global scale, the elimination of poverty has proved a far more effective contraceptive than the condom

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Drs Sharma and Sunderland comment:

Communications after the publication of our paper on the increasing medical burden of child abuse have saddened us by confirming both the increasing suffering and also the increasing amount of medical time which is being diverted from sick children by this small minority of families Although all demographic variables were represented, we could not refute the conclusion of others that most of the grievously maimed come from illegitimate and ill educated families [2] In Bradford, two thirds of proved abuse occurred in a small minority predicted to be at risk, and those receiving most attention from social workers and health visitors fared worst [3] We are aware of the authority which endows 'basic human rights' but are sufficiently aged parents to know that rights carry responsibilities. We have recently been asked by a teenage mother for help to attain two further pregnancies (in order to obtain more housing points), and, separately asked to advise a social worker who displaced a handicapped child from nursery because a stepfather had threatened to smash his baby's skull if it wasn't in the nursery within 24 hours. Hard cases require hard decisions Reviewing unpleasant options caused us professional discomfort but this was nothing compared with the real pain endured by these children It is no longer acceptable to blame 'the structure of society' nor is it acceptable to use our political beliefs to protect ourselves from examining received dogmas.

We are saddened that some professionals are still being sucked into the tempting option of sacrificing the child for the greater good of the family Paediatricians alone claim primary responsibility for the child's case—general practitioners usually serve the whole family and are under ethical restraints on disclosure; health visitors are trained to think of the whole client group/family, social workers by training and statute consider the family as the primary client. Only paediatricians consider the child's health as paramount and all else (including the family) as secondary to this

We trust that our representatives will note these figures and press for greater resources New strategies are needed to control this toll of violence. Child abuse has elicited spasmodic concern in the past and yet there is limited ability in the system to meet the needs of children in trouble, which is our paramount concern.

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ok reviews

ces in Pediatrics. Vol 34 Edited by arnass, A M Bongiovanni, G Morrow, a, and A M Rudolph. Pp 463: £45·00 ack Wolfe Medical, 1988 ISBN 1–0511–8.

opics covered in this American volume ather different from those covered by 986 *Recent Advances in Paediatrics*, overlapping in the three areas of l abuse, paediatric intensive care, and eonatal brain

e section on sexual abuse has a helpful nt of the paediatrician's examination clear black and white photographs, ding a full section on sexually trans- d diseases, the legal aspects in the ed States, however, differ from ours review on shock in the paediatric nt is clear, comprehensive, and bal- d. The chapter on treatment of viral ction—dealing with influenza, res- tory syncytial virus and the herpes ses—reviews the experimental work gives clear indication of clinical rele- ce There are three authoratative neo- l chapters on cerebral blood flow in tion to periventricular haemorrhage, monary oedema in premature babies, breast milk jaundice they contain full ounts of experimental work but have relevance for clinical practice. The s of oncogenes and suppressor genes in an neoplasia, tumour cell gangliosides, ects in carnitine and mitochondrial fatty d oxidation are not subjects that often ses the reviewer great anxiety (perhaps should) and these chapters are hard ding Nor does the pathogenicity of obic bacteria seem to be a major problem s side of the Atlantic There is a useful, ught provoking article on suicide Many rapeutic disasters result from the un- ical application of advances, none more than in neonatal medicine Strangely, excellent chapter on neonatal iatro- sis makes no mention of many of the plications of intensive neonatal care A ription of five programmes of children's ary health care was interesting but not levant for British readers Apparently hapter on therapeutic advances is a rent feature of these volumes and is xcellent review.

sections within articles are clearly d. The references are almost all ican and up to 1986. Reviews of advances need to be unbiased, interesting, clear, and relevant. This book mainly meets these criteria but some of the topics do not seem very relevant to a general paediatrician in this country At two thirds the price, the *Recent Advances in Paediatrics* is the better buy for paediatricians at all levels over here

G MCENERY

Lecture Notes on Immunology. By W G Reeves. Pp 197. £8·50 paperback Blackwell Scientific Publications, 1987 ISBN 0–632–00776–1

This book is an introduction to basic and clinical immunology for medical students and postgraduates. The style is annotated and deliberately didactic which is justifiable at this level Controversial areas are indicated on occasions, and this could have been done more often without detracting from the presentation Key words in the text are printed in bold type, which is useful for reference. Appropriately, suggestions for further reading lead mainly to other text books and reviews, though those wishing to pursue the subject would probably welcome a quide to the more important immunology journals.

The first chapter provides a concise overview, amounting to a definition, of the nature of immunology. The book then divides into two sections The first of these outlines, in eight short chapters, the components of the immune system and how they work Each chapter is clearly set out and illustrated with simple and informative line diagrams. Terms and concepts are well defined and explained Despite the divisional approach, the importance of cooperation between the components of the immune system in dealing with pathogens is strongly emphasised This emphasis is continued in the second section, which consists of six generally longer chapters on immunopathology The chapter on immunodeficiency will be of particular benefit to the trainee paediatrician. He or she could have argued, however, for more coverage of the protection of the infant by transplacental immunoglobulin, breast milk, and routine immunisation schedules, which have theoretical and practical implications for the whole of clinical immunology There is no separate chapter on the immunopathology of infection, but this is well covered throughout the text, with the notable exception of congenital infection There is no mention of the congenital transmission of the human immunodeficiency viruses in the short section on AIDS The value of the book, however, outweighs its deficiencies and can be recommended to those seeking a sound introduction to basic clinical immunology

G MORGAN

Clinical Trial Protocol Notes. Wessex Medico-Pharmaceutical Group Pp 116. £4 paperback. The Wessex Medical School Trust, 1987 ISBN 0–9512430–0–4

This model of a protocol for a drug trial is intended not only for trialists but for members of ethical committees It is most suitable for multicentre trials in adults but is also a useful guide for smaller single centre studies On the steering committee of 14 there is no paediatrician which is a pity as the legal and ethical issues of research in children differ from those in adults The protocol is set out as a form with section headings on the left hand pages, with guiding notes on the right, and covers all the appropriate aspects of a trial from subject selection, trial design, and statistical analysis to financial arrangements The appendices devote five pages to statistical design and 21 to ethical and legal issues of interest mainly to drug companies

This is a good *aide memoire* for anyone designing a clinical trial, whether it is to examine the effect of a drug or another treatment More emphasis could be placed on the proper enunciation of the hypotheses Is it proposed that new treatment is better than placebo or old treatment and the trial designed to identify confidently how much better the new treatment is? Or is it proposed that the new treatment is as good as the old one and the trial designed to show confidently that the new treatment could not be more than minimally worse than the old treatment and thus a reasonable substitute? Both hypotheses can of course be tested but it is important for the investigators at least to understand the questions.

The documentation of adverse events rather than the legal implications of such events also deserves more emphasis. One of the purposes of a clinical trial is to compare adverse events during drug treatment with adverse events occurring coincidentally or due to the disease irrespective of treatment. The patient of course must be informed of all reasonable anxieties about side effects However, it is not enough to say 'This treatment may make you sleepy or constipated ' It is better to say 'This treatment may make you sleepy or keep you awake; it may make you constipated or give you diarrhoea.' Discussion with the patient about serious and permanent side effects is a different matter.

At £4 this is a good buy It is not a substitute for a thorough understanding of the design of clinical trials, and ethical committees should not be persuaded that because an impressive and thorough protocol has been filled out the trial is necessarily scientifically valid

S MCKENZIE

Liver Disorders in Childhood. By A P Mowat Pp 408 £40 hardback Butterworth Scientific Ltd, 1987. ISBN 0407–0[illegible]-80–7.

This book is the second edition of a volume that first appeared in 1979 As such it has been completely revised and updated to include the major advances that have occurred in the intervening period. In addition, there is a new chapter on the subject of liver transplantation. It is written primarily for clinicians, especially paediatricians, paediatric surgeons, and gastroenterologists but it is also aimed at pathologists, biochemists, and laboratory research workers who are involved in liver disease in children A lack of clinical training will not inhibit easy understanding of the relevant sections, particularly those related to inborn errors of metabolism in which the biochemistry is explained in clear terms

The book can loosely be divided into three sections. The first two chapters deal with the anatomy and physiology of the liver and biliary tract, and the last two with the laboratory assessment and investigation of hepatobiliary and biliary tract diseases. These last two are perhaps best read before embarking on the bulk of the book that consists of 20 chapters that cover the whole range of disorders of the liver and biliary tract Some of these deal with conditions such as hepatitis and cholestasis in infancy, fulminant hepatic failure, chronic hepatitis, and cirrhosis which may arise from different aetiologies, others deal with disorders of related aetiology such as viral and non-viral infections, inborn errors of metabolism, and toxins. There are several chapters devoted to individual disorders such as Reye's syndrome, Wilson's disease, Indian childhood cirrhosis, and the complications of cystic fibrosis and sickle cell disease.

Written by an author who is pre-eminent in the field of childhood liver disease, it draws upon an unparalleled wealth of clinical material and is written in a clear style which is readily comprehensible to all who may wish to read it Each chapter is peppered with statements of fact that are clearly based on this experience and do not have the air of being unsubstantiated dogma which has been 'handed down from Galen ' A minor quibble is that biochemical values are usually (though not consistently) noted in conventional units and translated (occasionally incorrectly) into SI units I would have preferred the latter throughout but this does not detract from the value of this book as a welcome new edition that should be available in all departments of paediatrics

J ALLGROVE

Clinical Care of the Diabetic Child. By Allan L Drash Pp 135: no price stated, softback Year Book Medical Publishers, 1986

This book by the director of paediatric endocrinology at the Children's Hospital in Pittsburgh covers in 118 pages the epidemiology, aetiology, diagnosis, general outpatient management, and prevention of childhood diabetes By avoiding details of management it succeeds in travellin
across the Atlantic

There are many nice touches illust
the broad experience of the autho
both children with diabetes and the
ture (the book finishes with 200 refe
reflecting the recent literature up to
These include forthright statement
criminating between clinical and res
tools, and the use of immunosuppre
to prevent insulin dependent dia
mellitus in healthy children at high r
put firmly in the latter category

Despite its small size the book inc
reference to such fascinating specul
as the protective effect of breast fe
against development of diabetes mel
and the story of the Samoan children
moved

Treatment goals are clearly defined
our limitations in reaching them discus

The management approach desc
might be considered conservative or
istic; I find the emphasis on avoiding h
due to therapeutic over optimism at
tive; thus in Professor Drash's unit sp
care is taken to avoid hypoglycaemi
children under 5 years in case it lead
intellectual stunting, and before pu
most children with 'satisfactory meta
status' are on one injection of insulin a
'The primary hazard to the intensive in
approach' is noted to be 'failure resultin
frustration, disappointment' and the re
ing pressure to falsify records or abs
from treatment altogether is highlight

Mixed beef/pork insulins get a
press than we might give them, par
financial grounds, and the belt and b
approach to monitoring including gly
haemoglobin, capillary blood gl
monitoring, and regular 24 hour ur
glucose determinations will appeal to
children or their doctors in this count

If I was a child with diabetes I w
trust Professor Drash—he makes it
that despite my best efforts, achieving
normal metabolism with the limited
available is as much due to physiolo
luck as to family judgment This is a
introduction to current outpatient dia
care for students and junior doctors.

A-L KINM